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AN EXPERIMENTAL AND CLINICAL STUDY OF HISTIOCYTES IN ACUTE AND CHRONIC INFLAMMATION OF THE ACCESSORY SINUSES.*

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Sincere thanks are due the Research Committee of the Council of the American Academy of Ophthalmology and Otolaryngology for its generous grant of funds to continue animal work and histologic study of histiocytes during the academic year 1931-32, along lines reported before this Academy one year ago.† Many hundreds of serial sections were prepared from cat frontals and from selected human maxillary membranes. Detailed report of each type of experiment will be found herewith. Numerous agglutinative substances capable of arresting ciliary action were first tried, then certain alkaline earths and chlorids, and a limited number of human experiments based on the latter group were made.

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†Fenton and Larsell: "Reticuloendothelial Components of Accessory Sinus Mucosa. Arch. Otolaryn., 14:586, Nov., 1931.

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In cat material the histiocytes show trypan blue granules, due to vital staining. In human material the histiocytes show no granules, because vital staining is impracticable; but these cells are differentiated by Maximow's stain, by their grayish cytoplasm and their vacuoles, together with the characteristic appearance of the nucleus and the triangular or crescentic shape of the cell. Eosinophils and basophils show their characteristic granules in both human and cat preparations, staining much as in blood smears treated with Wright's stain.‡ All cat material was secured by needle puncture of the readily accessible frontal sinus, subsequent subcutaneous injection of 1 per cent trypan blue, and fixation of the acutely inflamed membrane after 48 to 72 hours, as heretofore described. Injected substances were of course autoclaved to prevent added infection.

CAT MATERIAL.

After injection of castile soap jelly, the entire mucosa is edematous, somewhat injected, and filled with pus cells, which have penetrated the epithelium until the latter is almost unrecognizable.

Thin glucose solution showed similar epithelial destruction, with mucosa filled with pus cells, but a few histiocytes in the deep part of the tunica propria.

A 50 per cent emulsion of cocoanut oil with agar showed some injury to the free ends of the epithelium, clogging of cilia, and considerable mucous secretion. The tunica propria was somewhat injected, otherwise nearly normal. Histiocytes in normal numbers, but numerous leukocytes; no very marked effect produced.

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‡Note on staining for histiocytes in human material.

Numerous requests for the technique of the so-called Maximow stain, with counterstain of hematoxylin, have been received. More details may be secured from McClung's Microscopical Technique.

Zenker-formal fixation is preferred; however, Susa gives excellent results. Sections should be from 6 to 8 microns.

The Delafield hematoxylin, not artificially ripened, should be about six weeks old. Make a very dilute solution of it by adding 2 to 6 drops to 100 c.c. distilled water; stain 24 hours. Wash in distilled water 24 hours. Result: chromatin is blue, cytoplasm either colorless or very light gray.

Place in azure II-eosin for 24 hours. Prepare as follows:

Stock solution A		Stock solution B	
Eosin, water sol., yellowish (W. G.)	0.5 g.m.	Azure II	0.5 g.m.
Distilled water	500 c.c.	Distilled water	500 c.c.

The stain:

Solution A, 10 to 12 c.c., according to material;

Solution B, 8 to 10 c.c., according to material;

Distilled water, 100 c.c. For the Susa fixed material used, best results were obtained by using 13 c.c. of Solution A and 8 c.c. of Solution B. Mix the eosin solution and water first, then add the azure solution. A noticeable precipitate should not form for several hours. Leave slides upright in the stain 24 hours. Transfer from stain to 95 per cent alcohol, then 100 per cent to differentiate and dehydrate. Finish dehydration in second 100 per cent alcohol, clear and mount. The differentiation takes place rapidly in 95 per cent alcohol, more slowly in 100 per cent.

Chromatin of the nuclei is dark blue, nucleoli are purple, and leukocyte granules are differentially stained in colors corresponding to those given by Giemsa. O. L.

Jelly of chondrus crispus (which contains a good deal of salt) showed some parts of the membrane injected with blood and considerably thickened, while the tunica propria was full of leukocytes, with a few histiocytes. Elsewhere the mucosa was completely destroyed, with a great mass of pus in the sinus cavity surrounding shreds of the moss.

Mucilage of tragacanth (without the usual preservative addition) caused little injection or thickening of the mucosa. The epithelium was somewhat damaged, with clumping and occasional destruction of cilia. There was considerable mucous secretion with enlargement of goblet cells. Pus cells were frequent in the tunica propria, migrating through the epithelium, and in the gum out in the sinus cavity.

Thick glucose left the sinus membrane of normal thickness, neither edematous nor injected. The epithelium was fairly normal in appearance, but the cilia were badly gummed together. Goblet cells were numerous and large, with an abnormal amount of mucous secretion. Some leukocytes and about the normal number of histiocytes were found in the tunica propria. The chief effect was apparently clumping and apparent stasis of cilia, and production of a large amount of mucous secretion.

Milk of magnesia produced very great numbers of histiocytes, but the epithelium was largely destroyed.

A repetition of the experiment with chondrus crispus, permitting a longer time to elapse, gave much the same result as before. The epithelium became so infiltrated with leukocytes as to be almost unrecognizable. Many lymph follicles were found in the tunica propria, pressing up on the epithelium. It was hard to recognize the histiocytes, but they were not numerous.

Petrolagar with 10 per cent glycerine left the epithelium intact. Some lymph follicles were found under the epithelial layer, wherein the goblet cells were much swollen. Numerous histiocytes were present.

Calcium hydroxide 5 per cent, emulsified with 0.5 per cent agar, showed the cilia destroyed and much epithelial damage, with marked migration of leukocytes through the epithelium. The tunica propria showed many polymorphonucelar cells, some lymphocytes and plasma cells, and large numbers of histiocytes. The latter were scattered through the edematous tunica propria, appearing to be migrating toward the epithelium.

Calcium lactate 1 per cent with gelatin 1 per cent caused bad destruction of the epithelium in spots. The mucosa was thick, edematous, and full of various types of cells, including numerous

lymphocytes, some polymorphonuclears, some plasma cells, and very numerous histiocytes, especially just beneath the epithelium. In spots where the epithelial cells are nearly destroyed, the histiocytes form a continuous layer at the base of the epithelium (see Fig. 1).

Sodium phosphate 1 per cent with 2 per cent gelatin gave a relatively normal mucosa, somewhat swollen in spots, but not very edematous. The cilia remained well shown. A somewhat higher number of histiocytes than usual occurred in the tunica propria. The edematous areas contained some polymorphonuclears and a few plasma cells. A control animal in which plain gelatin was used died from infection, and the tissues were not prepared.

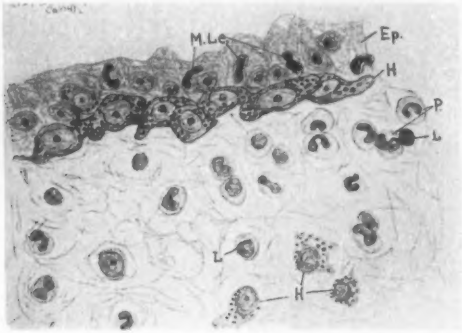

Fig. 1. Frontal sinus membrane, cat. Sinus had been injected with calcium lactate 1 per cent in 1 per cent gelatin. The animal then received subcutaneous injection of 0.5 per cent trypan blue in normal saline. A barrier of histiocytes is clearly seen under the damaged epithelium. Fixed after 48 hours; stain, hematoxylin-eosin-azur. Camera lucida drawing, 10 oc. 90 obj. (oil immersion) (Larsell). Ep. epithelial cells; M. Le. migrating leukocytes; H. histiocytes containing trypan blue granules; P. polymorphonuclears; L. lymphocytes.

Scarlet red 5 per cent oxyquinoline sulphate 2 per cent, as used for stimulation of skin grafted areas, caused mucosal edema and epithelial damage, with patchy loss of cilia. Leukocytic migration was occurring through the epithelial layer, and the tunica propria was full of pus cells. Very few histiocytes were present.

Dichloramin 2 per cent in chlorcosane was responsible only for unusually large goblet cells, other findings being normal. This experiment should be repeated, as double penetration occurred, with but little oil in the small frontal, while epidural hemorrhage caused death of the animal.

One animal was injected on the right side with a virulent hemolytic upper respiratory streptococcus in semiliquid gelatin culture. The left side was studied as a control. Two days after the sinus

had been infected, 1 c.c. of vaccine made up from the same organism was injected intradermally after the method recently introduced by Corbus. Another injection of vaccine was given two days later, and after two more days trypan blue was injected and the material was fixed. The infected sinus showed slight hyperemia when dissected out. In section the membrane was hyperemic and edematous, the epithelium tall, with many mucous cells. The subepithelial tissue contained many histiocytes and plasma cells; and in spots numerous lymphocytes and leukocytes, with great thickening of the mucosa and epithelial layer. At such areas, the epithelial cells were elongated and devoid of cilia, and the layer of mucous secretion normally covering the epithelium was absent. Apparently the infection had passed at these points into the underlying tissue. Leukocytes in considerable numbers were migrating through the epithelium, and masses of pus were found in some parts of the sinus cavity. The fibroblasts were more frequent than normally in the tunica propria. At other points of the infected sinus transitional stages from the marked infection just described occurred, grading into nearly normal thin ciliated mucosa with few goblet cells. At such spots, the tunica propria seemed to contain rather more than the normal number of histiocytes.

The control (left) side was entirely normal except for a very definite increase in the number of histiocytes, also a few plasma cells. These findings, apparently confirmatory of the assertion of Corbus that intradermal vaccines stimulate histiocytic defense wherever inflammatory lesions are found, should of course receive numerous experimental confirmations before they can be accepted.

HUMAN MATERIAL.

Individuals with apparently equal involvement, clinically and radiologically, were subjected to various types of local treatment; and after the lapse of a certain time, varying with the needs of each case, the membranes were carefully removed at radical operation, fixed immediately, and examined under the eosin-azur differential stain for histiocytes and other elements.

Case 12707, used to clarify points of technique, had areas of broken down epithelium with subjacent edema; elsewhere the usual tall columnar cells with numerous goblet cells occurred, and the edema was much less, and the tunica propria fibrous. Under the broken areas were numerous plasma cells, some round cells and some histiocytes. Under intact epithelium, lymphocytes predominate, occasionally as small follicles. There are also numerous fibroblasts and occasional basophil cells.

Case 12129 presented an intact epithelium with no migration of leukocytes and little edema. The tunica propria was fibrous but rather thin, and filled with very great numbers of plasma cells. Comparatively few histiocytes were found. These plasma cells formed a definite, though not compact layer beneath the epithelium (see Fig. 2).

Case 11432, left side, had received a few washings with normal saline solution. Here the epithelium was tall, and cilia absent in patches, elsewhere clumped, occasionally normal. Very many mucous cells and migrating leukocytes were found. The tunica propria was very edematous, containing numerous lymphocytes, many plasma

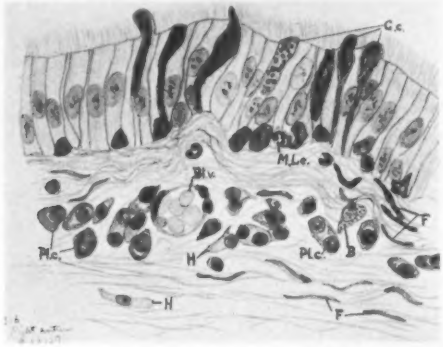

Fig. 2. Maxillary antrum membrane, human, Case 12129, removed at radical operation. Plasma cells predominate in this very fibrous membrane, and histiocytes are few. Hematoxylin-eosin-azur. Camera lucida drawing, 10 oc. 90 obj. (oil immersion) (Larsell). G. c. goblet cells; M. Le. migrating leukocytes; Bl. v. blood vessels; B. basophil; H. histiocytes, showing white vacuoles in gray cytoplasm; Pl. c. plasma cells; F. fibroblasts.

cells, and an occasional mast cell. Very many eosinophiles, some histiocytes and many fibroblasts completed the picture (see Fig. 3).

The right side, clinically identical, received one 6 c.c. injection of milk of magnesia. No epithelium was visible in these sections; there was marked hemorrhage. The tunica propria was dense and fibrous and the predominant cells were fibroblasts. It is not unlikely that the radiologic and clinical similarity of these two sides were due to the thick fibrous repair on the right, and that merely the hemorrhage may be laid to the magnesia.

The right antrum of D. H. was injected with milk of magnesia once or twice a week for two months. This membrane was markedly edematous. Lymphocytes were very numerous about the blood vessels. Plasma cells were numerous, especially about the mucous glands

in the deep part of the mucosa. Very numerous eosinophiles were found near blood vessels and in the tunica propria where epithelium was missing. Histiocytes were fairly frequent, and some fibroblasts were scattered through the tunica propria. Certain pigmented cells were evidently degenerative. The tall epithelium showed almost every other cell a goblet cell, indicating degeneration; but most of the epithelial cells were still ciliated. Here and there the epithelium was lost, and much mucous secretion was present. A few almost normal patches were found.

Very different was the left antrum in the same case, washed for two months with normal saline. This was much more edematous,

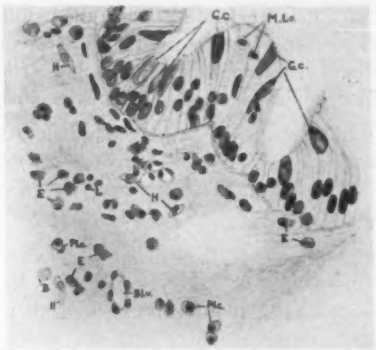

Fig. 3. Maxillary antrum membrane, human. Case 11432, removed at radical operation. Marked edema of the tunica propria and very great numbers of eosinophils. Hematoxylin-eosin-azur. Camera lucida drawing. 10 oc. 40 obj. (Larsell). G. c. goblet cells; M. Le. migrating leukocytes; H. histiocytes; B. basophils; E. eosinophils; Pl. c. plasma cells; L. lymphocytes; Bl. v. bloodvessels.

with large spaces in the tunica propria waterlogged by fluid. There was marked infiltration by lymphocytes, with patches of lymphoid tissue. The epithelium was markedly degenerated in spots, with cilia absent from considerable areas; elsewhere normal, save for unusual quantities of secretion, with half the cells goblets. Where the epithelium was degenerated, very little secretion was seen. Plasma cells were more numerous than other types, save for the perivascular lymphocytes in the tunica propria. Few histiocytes were to be found, and no eosinophiles. This raises the question whether the marked eosinophilia of the right side was due to the long exposure to the milk of magnesia, by chemotaxis, or by dehydration changes in the mucosa. Certainly there was a striking absence of eosinophiles in the left side, where normal saline was used.

RECAPITULATION.

In the cat, destructive changes in the mucosa of the frontal sinus, without any apparent increase in the histiocytic defense, were produced by soap jelly, thin and thick glucose, cocoanut oil with agar, chondrus jelly, mucilage of tragacanth, and scarlet red with oxyquinoline sulphate.

Certain kations produced notable increase of histiocytes in the membrane, in spite of loss of cilia and more or less epithelial damage. These substances included calcium hydroxide 5 per cent in 0.5 per cent agar; calcium lactate 1 per cent in 1 per cent gelatin; and sodium phosphate 1 per cent in gelatin 2 per cent. Especially interesting is the calcium lactate effect: the epithelium badly destroyed in spots, under which a continuous layer of histiocytes has formed (see Fig. 1). Numerous lymphocytes, some plasma cells, and some polymorphonuclears are found in the edematous stroma.

Human material was secured by radical antrum operation on certain individuals with apparently equal involvement on each side, both clinically and radiologically. This material was divisible into three histologic classes:

1. Fibrous repair, associated with which plasma cells were observed in large numbers (see Fig. 2).

2. An apparently allergic type, with much edema and many eosinophils, and slightly greater numbers of histiocytes and plasma cells than normal (see Fig. 3).

3. Mixed types, varying apparently with the location, conformation and healing of chronic inflammatory lesions.

The time factor in human material was introduced by washing one antrum with milk of magnesia, the other with normal saline, for two months once or twice weekly. Marked edema, with very numerous perivascular eosinophiles, fairly numerous histiocytes and some fibroblasts, characterized the "magnesia" side. On the "saline" side, edema was excessive, with marked lymphoid infiltration and loss of cilia and of epithelial patches. Numerous plasma cells were found about mucous glands, with but few histiocytes and no eosinophiles.

Intradermal immunization (after Corbus) was attempted on a cat which had been infected in one frontal by a virulent gelatin culture of hemolytic streptococcus. Both the normal and affected side showed many more histiocytes than normal, seeming to corroborate Corbus' theory that intradermal vaccination activates histiocyte defense at points of inflammation throughout the body.

CONCLUSIONS.

Subject to further experimental confirmation on human subjects, it would seem that local use of solutions or suspensions of alkaline-earth salts or hydroxides (calcium, magnesium) favors the mobilization of histiocytes in acute inflammation. Oily and colloid substances are destructive of epithelium and favor infection by impairing ciliary action, necessitating invasion of the subepithelial stroma by polymorphonuclear cells without any increase in the number of histiocytes. The chlorides seem to favor edematous changes with marked increase of lymphocytes. An increase of plasma cells seems to accompany long-standing fibrous changes.

The Department of Radiology and Department of Anatomy are now engaged in a series of experiments on cats to provoke chronic inflammations of the frontal sinuses, upon which the X-ray will later be used.

Further experiment, to determine the influence of acid, saline and alkaline diet, to check further the merits of intradermal vaccine treatment, and to decide on the function of the plasma cell, is necessary and will be undertaken when necessary funds for technical help and material are available.

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INFECTION AND RESISTANCE IN THE UPPER RESPIRATORY MUCOSA.*

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The mucous membrane lining the upper respiratory passages must be regarded as a complicated mechanism which may be affected adversely or favorably by many factors from the outside world. One factor may be relatively important in the defense of the membrane against bacterial invasion but to emphasize it to the exclusion of others is to be misleading. In order to relegate each idea to its proper place and establish its relative importance it is necessary to consider the problem of infection and resistance as a whole. The following is an outline of the factors which should be taken into consideration:

I. Resistance of the mucosa to invasion.
   1. Mucus secretion.
   2. Ciliary action.
   3. Phagocytosis.
   4. Lysozyme.
   5. Local reaction.
   6. Natural immunity.
   7. Local immunity.

II. Invasion.
   1. Decreased resistance to bacterial invasion.
      (1) Diet.
      (2) Physiological effects.
         a. Chilling.
         b. Ventilation.
         c. Chemical irritation.
         d. Metabolic fluctuations.
      (3) Allergy.
   2. Properties of the micro-organism affecting invasion.
      (1) Toxic products and their effects.
      (2) Capsule formation.
      (3) Adaptability to environment.
      (4) Ability to lodge in intracellular spaces.

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The subject can best be considered from the standpoint of resistance and the factors which tend to overcome it. Since infection is the result of a disturbed balance between the parasite and host, the factors which decrease host resistance will have the same effect as those which augment the invasiveness of the parasite. Furthermore, in order to take into consideration all the known processes brought into action, it is necessary to follow the infection through to its ultimate conclusion, whether recovery, chronic infection, latency or death. It is the purpose here to give special attention to factors affecting or closely related to the mucosa.

THE DEFENSE MECHANISM.

1. *Mucus Secretion.* The protective influence of mucus on the epithelial surface has been much discussed but perhaps its significance has not been fully realized. Infection invariably results, with participation even by the weaker pathogens, when mucus secretion has been greatly reduced or is absent. In experimental xerophthalmia, for example, Mori[1] found mucus cells of the conjunctiva all destroyed, with shrinkage of secretory cells in the ascini of the lacrimal gland. There was little or no evidence of secretion. Cystic dilatation of the ducts of the torsal glands was found with a xerotic process in the epithelium of the duct and lid margins. An eye of this type is always infected; frequently by bacteria that are ordinarily harmless. He also found the lack of vitamin A causing in the same animals a destruction of the mucus cells in the mucous membrane of the larynx and trachea with the mucus cells in the submucosa functioning little or none. Inflammation and infection followed such changes with death from bronchopneumonia. Little or no secretion from the salivary glands in many of the rats resulted in a dry mouth, accompanied by an increase in the number of bacteria and infection.

Cramer and Kingsbury[2] found avirulent infections constant in vitamin A deficiency. Seven such rats were cultured from the heart's blood and four were found to contain bacteria. They conclude that general humoral defenses are not weakened by such deficiency and therefore a weakening of the local defense, represented by decreased secretion from the mucus surfaces, is primarily responsible for the invasion.

Findley[3] was able to prevent the onset of experimental keratomalacia in vitamin A deficient rats by bathing out the conjunctival sac with tears. Fatiguing the secretory cells by pilocarpine stimulation hastened the onset.

An effect quite similar to vitamin A deficiency is produced by exposure to X-ray or radium. Atrophy of the secretory structures results.

A mucous membrane responds to irritation by increased secretion. If a virulent organism attempts to gain entrance to the membrane by paralyzing ciliary activity or destroying membrane cells through diffusion of toxic products, it is compelled to work against the current of outflowing mucus. Usually the bacterium will be carried beyond its portal of entry toward the stomach. Regardless of the mucus flow the interposition of greater distance between the organism and membrane is a temporary protection should the mucus current be stopped by paralysis of ciliary activity. A secretion of mucus beyond a given optimum rate, however, must be regarded as detrimental. The mucus current must be kept moving and it is evident that if the layer becomes too thick the top portion will begin to lag or even flow in the opposite direction under the influence of gravity. A stagnation of secretions thus would result. It has been observed that breathing ammonia causes an increased secretion of mucus and when breathed freely often results in tuberculosis of a fatal type. A decrease in viscosity of the secretion is probably just as important in this connection as the increase in amount of secretion.

In the light of available evidence, such a thickened mucus layer is only a temporary protection against many bacteria. Even a very short delay, however, may enable the membrane to recover sufficiently to gain the upper hand, if it is sufficiently responsive.

It has been shown[4] that sinus secretions of the rabbit inhibit the growth of a lysozyme susceptible bacterium for five to six hours but after that a rapid increase in numbers occurs in the presence of the secretions. Several investigators, including Goldsworthy and Florey,[5] Neucki[6] and Mayer,[7] have grown bacteria on media containing mucus from different sources. The mucus itself is a poor medium for the growth of bacteria but if the mucus stands in contact with the dead body or over an area of inflammation for several hours a sufficient amount of tissue fluid is taken up, as a result of increased permeability of the membranes, to support a quite luxuriant growth.

Evaporation is a factor of great importance in the regulation of the secretory mechanism of the respiratory mucosa. Expired air is practically saturated, so the lower the relative humidity of the inspired air the greater the water loss from the mucosa per day. This loss has been estimated under ordinary circumstances to be about one quart. The fact that the air is dry is probably not in itself detrimental so long as the increased water loss is compensated by an increased intake. Otherwise the practice of sending patients with

lung disease to dry climates would be detrimental. Certainly the incidence of upper respiratory infections is no greater in arid regions than in many of the more humid regions, which could be taken as some indication that dryness in itself is not measurably harmful. Repeated sudden changes on the other hand may lessen the sensitivity of the secretory mechanism to proper stimuli.

The temperature of the mucosa is regulated by the amount of blood flow through it. Inspired air soon reaches body temperature in its passage through the nasal cavity. The amount of blood flow is controlled by a delicate vasomotor mechanism. Mudd, Goldman and Grant[8] found that chilling of the body surface produces ischemia in the mucous membrane of the palate, tonsils and oropharynx. A profuse discharge of mucus occurred from both sides of the nose when a wire was introduced into one side. The discharge was affected little or none by a diminution of blood supply and shrinkage of the nasal mucous membrane in response to chilling. The vasoconstrictor reflex was slower for the nasal and nasopharyngeal mucosa than for the skin of the forehead.

McDonald, Leisure and Lenneman[9] found that stimulation of the frog epithelium by ephedrine or epinephrine produced, in addition to a speeding up of ciliary activity, a thick mucus, which, however, did not prevent the acceleration of speed of particles on the surface until a considerable amount had been secreted.

Mucus consists of water, mucin, inorganic salts, epithelial cells, leukocytes and granular matter. Other conditions being favorable there is sufficient nutrient material present for ordinary bacterial maintenance. The osmotic pressure of the fluid is equal to that of the body fluids and the reaction slightly alkaline or neutral. Most of the pathogenic organisms found on the respiratory mucosa are not able, however, to make use of mucin directly as a source of nitrogen. The viscid, colloid character of the mucus is dictinctly unfavorable. Mucus disperses itself in water without dissolving, according to Miller,[10] and in aqueous solution is very viscous even in great dilution (Levene[11]). Waksman[12] states that colloids, as for example gelatin and gum arabic, have an inhibitory effect upon the secretion of the enzyme invertase. Mucus may have a similar effect toward bacterial enzymes. Waksman and Starkey[13] found the combination of proteins with certain nitrogen-free substances rendered them much more resistant to bacterial decomposition. Furthermore, on the upper respiratory mucosa the movement of the mucus in the ciliary current, and the presence of phagocytes and lysozyme render conditions particularly unfavorable.

Mucin is a glycoprotein made up of a protein group, which according to Levene[11] differs widely from tissue to tissue, and from species to species; and of a carbohydrate group which decomposes into acetic acid, sulphuric acid, glucosamine and glycuronic acid. Splitting of this molecule, therefore, would result in the production of considerable quantities of acid which would be distinctly unfavorable for most of the pathogenic bacteria of the mucosa. Of course the buffering effect of the protein, and rapid absorption from the mucous surface, would rapidly remove the acid from solution.

Mucus secretion makes possible the surface activity of phagocytes which many claim to be the principal defensive mechanism. Mucus is certainly the first line of defense and makes it possible to bring into play some of the other most important defensive measures. The mucous layer of the epithelium may be compared to the capsule of a bacterium, which is greatly protected by the surrounding layer. It has been shown that inagglutinable encapsulated strains are rendered susceptible to agglutination when the capsule has been removed by treatment with bile. Similarly resistant strains may be rendered susceptible to bacteriophage by removing the capsule. Most of the potential infections of the mucous membrane are prevented or warded off by the enveloping "capsule" of mucus.

2. *Ciliary Activity.* The relation of ciliary activity to mucus secretion, in the prevention of bacterial invasion, has already been referred to. It is evident that if the cilia are to accomplish anything in a protective way they must have a liquid menstruum in which to act. A viscid menstruum has decided advantages in holding foreign particles firmly in place while they are being "esculated" to the point of removal. The length of the cilia in the human is such that they could have very little effect on air currents either in the sinuses or nasal cavity. This is especially true since they are acting in a liquid medium.

There are a number of factors which are known to affect ciliary activity and no doubt there are others. Careful physiological studies on the mechanism of ciliary activity have been made by Gray,[14, 15] Inchley,[16] Greve and Schmidt,[17] Bhatia,[18] McDonald, Leisure and Lenneman,[9] Merton[19] and others. In general, cilia function in much the same manner as muscle and are subject to similar limitations and methods of control.

Any factor which stops, or decreases, the rate of ciliary activity, predisposes to stagnation of secretions and infection at the point of stasis. Time is an important element and even a temporary stasis may be sufficient to allow a virulent micro-organism to gain a foot-

hold. The host is then thrown on the defensive and in a much less favorable position. Some of the factors which affect the rate of activity are as follows: temperature, nervous control, H-ion concentration, electric stimulus, proper ionic balance and possibly a number of others either directly or indirectly, such as endocrine dysfunction, bacterial toxic products and local hyperemia.

Proetz[20] has brought out very clearly the relative importance of ciliary action in maintaining healthy nasal function. The fact that an antrum magnified in proportion to cilia a foot long would hold enough water to supply the city of New York 14 years and 4 months, and yet would be completely cleared out by the cilia in a few hours time, is ample testimony as to their mechanical prowess and efficiency. It is difficult to see how any bacterium could penetrate such a barrier even when actively motile but we know that penetration occurs frequently by nonmotile organisms. Something must occur to reduce the efficiency of the cilia and mucus layer and it would appear in the light of available evidence, to be presented later, that a sufficiently virulent bacterium in itself is able to bring about changes in the mucociliary layer which permit its penetration.

There is no general agreement on the exact mechanism of ciliary action. It will be necessary to have a clearer conception of the process in order to understand thoroughly any effect which bacteria may have. Gray[14] believes that the bending force in the cilium may be due to changes in the distribution of water in the cilium. This he thinks may be brought about by a shift in hydrogen ion concentration and a consequent change in hydration on one side of the cilium. In studying ciliary movement from the standpoint of the energy cycle he found: *1.* That the cell must have a considerable energy reserve since it continues activity several days after excision. *2.* That movement gradually slows, but is quickened by substances which accelerate the formation of lacticogen from glycogen in muscle, such as the addition of K or veratrin or the removal of Mg. *3.* That exposure to hydrogen ions slows the beat and reducing the Mg++ quickens it, reactions which are reflected in the oxygen consumption. *4.* The mechanism of bending is due to the production and removal of H-ions, a reaction which occurs only in the presence of calcium and a supply of energy, while in the absence of calcium, energy is expended without movement. *5.* Since ciliary movement stops 45 minutes after the removal of oxygen, and begins again after O_2 is restored, the process may be considered an anaerobic one with O_2 necessary for the removal of waste products.

Most of the recent workers agree that ciliary movement is to some extent under nervous control. This hypothesis is supported by

McDonald, Leisure and Lenneman,[9] Merton,[19] Seo,[21] Bhatia,[18] Grutzner, Kraft and Parker, and Gothlin. Grave and Schmidt[17] and Bhatia[18] found connections between the ciliary rootlet and the basement membrane. Seo[21] found acceleration of movement of frog cilia by dilute solutions of acid, alkali or quinine, by temperature of 50° C. or 2° C., by weak induced currents, or by mechanical stimuli when applied to the surface of the tongue. Section of the ninth nerve prevented acceleration by the above stimuli when applied to that side. Other observations indicated the presence of a reflex center in the medulla with motor fibres in the nervus palatinus. .The reflex response was bilaterally symmetrical with 1 sec. latent period. Merton[19] finds that the ciliated epithelium of Planorbis is brought to a standstill by 0.1 M $CaCl_2$ and that activity is regained in 0.1 M Kcl. He also finds that the mechanism of the human ciliated epithelium is under the influence of the nervous system. These observations suggest the importance of further studies on the effect of bacterial products on ciliary action either directly or through nervous stimulation.

3. *Phagocytosis.* The wall of phagocytes which meets any bacterial invasion or threatened bacterial invasion of the body may be regarded as the second and not least important line of defense. The mobilization of phagocytes to surround a foreign substance takes place readily in any part of the body, but in the upper respiratory tract it is especially important.

Leukocytes have been described as normal constituents of nasal secretions since the early days of bacteriology. In some unpublished work done at this laboratory by Linton and Dixon nasal smears from 54 hospital patients not on nose and throat service were examined cytologically and bacteriologically. These patients were not complaining of nose and throat trouble. Only 30.5 per cent of these showed no leukocytes and it seems probable that scantiness of material on the slide might account for failure to find cells in many of these. Many to a large number were found in 45 per cent of the 108 smears and few to none in 55 per cent. It was observed that absence of neutrophiles did not indicate a sterile mucosa and that about 50 per cent of the smears showing large numbers of neutrophiles proved to be sterile. These smears and cultures were taken in July.

There seems to be a growing impression that the histiocyte is one of the most important factors in the defense of mucous and serous membranes against streptococcic invasion. Gay and Morrison,[22] 1923, in experimental empyema often noted a preponderance of large mononuclears in the exudate of immunized animals on reinoculation of multiples of the fatal dose of streptococci. In the course of a fatal infection there was a preponderance of polys. Furthermore,

they state that when doses of streptococcus are inoculated intradermally at given intervals, the protection is better against intradermal than against intravenous or intrapleural infection and, similarly, intrapleural immunization protects better against intrapleural infection. They identified histiocytes in the pleural exudate by mixing it in equal parts with 0.1 per cent aqueous neutral red. The dye may be restored from brown to red by adding 1-1000 Hcl to a Ph of 6.2-6.4. Rabbits were protected against intrapleural infection with hemolytic streptococcus by injection of a salt and peptone-free broth concentrated ten times. The bacteria in such cavities decreased rapidly until they were sterile in six hours. The immune animals, 24 hours after infection contained more clasmatocytes in the cavity fluid than normal infected animals. Four animals injected with 3 c.c. each of concentrated broth showed an average leukocyte count after 24 hours of 13,800,000, with 45.7 per cent clasmatocytes. An exudate rich in neutrophiles did not protect against hemolytic streptococcus infection. They express the belief that the clasmatocytes come from the adjacent connective tissue and not from the blood stream. The outcome of experimental streptococcus infection depended on the number of clasmatocytes present and not on the number of polymorphonuclears.

Lewis and McCoy[22] have shown that clasmatocytes have a superior property of resistance outside the body. They would, therefore, be better adapted to the defense of a mucous surface.

Cunningham[24] and MacCallum[25] in studying the resorption of pigment granules and bacteria from the peritoneum refer to the importance of phagocytic properties of cells of the serosa and the endothelial lining of the lymph vessels. Colon and anthrax bacilli injected intravenously have been shown by Werigo and Adami, and also Abbott and Nicholson, to be largely disposed of by the Kupfer cells of the liver. Nagao[26] found liver endothelium to be the most important factor in the disposal of streptococci in the guinea pig, while Manwaring and Fritschen[27] found tissue affinity for bacteria in the liver increased by immunization. Gay[28] states that in subacute localized inflammation, particularly when due to streptococcus and in the process of healing, macrophages are very abundant. He believes the importance of macrophages in the disposal of bacteria has been underestimated.

Gay and Morrison[22] observed that actively immunized pleural cavities with little or no exudate and no clasmatocytes were highly protected. The material used to produce an exudate was found to be less important than the time element involved. An influx of polymorphonuclears is an early phase of septic or aseptic inflammation

and is followed by mononuclear cells which arrive with varying rapidity, depending on the virulence of the organism.

Gay, Clark and Linton[29] after intrapleural injection of aleuronal-starch mixture in rabbits observed a thickening of the parietal pleura which was marked in 10 hours and reached 63 microns in 18 hours. After three days the serosal layer was intact and under it was a dense layer of mononuclear cells extending down and forming compact nodules about the blood vessels. Very few polymorphonuclears remained. Injection of 125-300 million streptococci into 18-hour cavities, prepared in this manner, showed a drop in the number of streptococci to one-half within 12 minutes, with a decrease in the number of polymorphonuclears and an increase in the number of clasmatocytes. Both types of cells then increased for six hours with a return to normal in 24 hours. Cultures were sterile in 24 hours. Phagocytosis by clasmatocytes was very active in the early periods (12-30 minutes). There was one one-sixth as much phagocytosis by polymorphonuclears. When a fatal dose of streptococcus was injected, there was a steady increase in the number of bacteria in 24 hours, with only slight phagocytosis, mostly by clasmatocytes. There were hemorrhages and destruction of serosa within two hours, rather scanty cellular elements with mononuclears better preserved, and necrosis of the pleura in 24 hours. Thickening of the parietal pleura by the third day was due to clasmatocytes as shown by vital staining with trypan blue.

Early workers found mononuclear cells predominant in the lesions of erysipelas. The mononuclear response to streptococcus injection in monkeys was found of prognostic significance by Zangemeister and Gaus.[30] Weil[31] concludes that fixed tissue cells are responsible for streptococcus resistance. Hopkins and Parker[32] found phagocytosis by endothelial cells of the lungs an important factor in resistance against streptococcus in the cat. Levaditi[33] observed that streptococcus infected war wounds have a tendency to clear up at irregular intervals and such wounds have the power of rapidly destroying large numbers of the same kind of streptococci. Granulation tissue contains many clasmatocytes. Gay[34] believes that cellular response explains local tissue immunity and that the tissue cells become more resistant, rather than desensitized.

Fenton[35] in studying the "reticulo-endothelial" components of the accessory sinus mucosa of the cat found very few histiocytes in the normal membrane as determined by vital staining. Mechanical trauma and injection of hemolytic streptococci caused a marked accumulation of histiocytes, while a combination of trauma and injection of hemolytic streptococci caused an intensification of the process. Warm

paraffin and 20 per cent acacia caused some slight increase in histiocytes, but reticulin, a histiocyte extract, injected subcutaneously following local trauma and injection of streptococci in the sinus, caused a great preponderance of polymorphonuclears to accumulate in the sinus. Fairly numerous histiocytes were observed in human pathological membranes removed by Caldwell-Luc. Fenton[36] also stated that "sterile inflammations have been produced with increased resistance to bacterial invasion due to the presence of a protective layer of leukocytes." Some of the good results from radical operation he believes are due to trauma and not to the removal of infective foci.

Tunicliff[37] found weak colloidal suspensions of cholesterol to increase phagocytosis in vitro and to neutralize the depressing effect of diphtheria toxin on phagocytosis. In another piece of work,[39] she found a marked increase in phagocytosis of hemolytic streptococci after intravenous injections of calcium gluconate, glucose, sodium iodide and sodium salicylate, into rabbits.

Dameshek[38] says that histiocytes tend to appear wherever there is a marked monocytosis, 12 per cent or more, except in severe septicemia. He believes that they constitute a secondary line of defense against bacteria and may be associated with the development of immunity.

Mueller[40] showed that the number of leukocytes found in any vascular region depends upon the balance between the two portions of the autonomic nervous system. There is a periphero-splanchnic balance, with sympathetic stimulation resulting in vasoconstriction and local leukopenia, while parasympathetic stimulation causes vasodilation and leukocytosis. Nervous activity is always the primary cause of an increase or decrease in the number of leukocytes. He points out that in insulin shock there is peripheral dilatation, increase in endothelial permeability and other signs of parasympathetic overstimulation, accompanied by a great increase in leukocytes.

4. Lysozyme. Although Fleming[41] found the lysozyme content of nasal mucus to be considerable, it is questionable whether it plays a significant role in controlling bacterial growth on the mucous surfaces. Thomson and Hewlett found nasal mucus nonbactericidal but found that it exerts an inhibitory action on the growth of microorganisms. Goldsworthy and Florey[5] concluded that the protective properties of mucus are more in its mechanical properties than in its ability to destroy bacteria. Findlay[3] found the lysozyme content of rabbit tears reduced by a Vitamin A deficient diet.

Lysozyme was found in all the human tissues and secretions examined by Fleming[41] except urine, sweat and spinal fluid, although

the concentration varied considerably. Using tears as an arbitrary standard of 100, Ridley[42] points out that nasal mucus contains 33, sputum 33, leukocytes 100, pus 5, saliva 1 and egg white 200. It must also be kept in mind that although lysozyme is very effective against certain micro-organisms, particularly some of the saprophytic bacteria from the air, it has little or no effect against some of the bacteria of greatest importance in the respiratory tract. Wolff,[43] using a concentrated lysozyme diluted to 1/5 to 2 times egg, found that it had no effect on the streptococcus viridans, pneumococcus, diphtheria bacillus or colon bacillus. The staphylococcus, hemolytic streptococcus, meningococcus and tubercle bacillus were affected about equally and to a moderate degree. However, the concentration of lysozyme found in nasal mucus and sputum is not sufficient to offer more than a very mild, temporary inhibiting effect.

Ridley[42] observed that pus is the only pathological fluid containing much lysozyme. Fleming[41] found that resistant strains may be developed by continued cultivation in the presence of lysozyme, a factor of great importance in the upper respiratory tract, where constant contact of the organism with the secretions would afford ideal conditions for the selective development of resistance.

The indications are, therefore, that lysozyme plays a minor part in the resistance of the upper respiratory mucosa to invasion.

5. *Local Reaction.* It is a general principle of surgery that an acute inflammatory process should not be operated, on account of the danger of opening up pathways for the spread of the infection. This holds equally true in surgery of the ear, nose and throat. The full extent of the processes taking place which make it relatively safe to operate on a process which has "quieted down" are not fully understood. It is clear, however, that since similar results follow similar surgical procedures in various parts of the body, the local "walling off" process has points of similarity wherever it may be found. In general, there is a piling up of cells most resistant to the infection. The cells which are most readily mobilized are the polymorphonuclears. They quickly reach the site of infection and tend to isolate it from the surrounding normal tissue in a mechanical way, as well as to phagocytose the bacteria, and for the time being render them relatively harmless.

If the infection continues long enough there may be thickening of a surrounding membrane, as in empyema, or the production of a pyogenic membrane, as in staphlococcus infection. Infiltration of monocytes occurs as the condition becomes chronic. The histiocytes are especially resistant to unfavorable influences. There may form,

in the older processes, a surrounding wall of connective tissue, which is also highly resistant to extraneous influences. It is interesting to note the origin of one group of histiocytes from connective tissue in view of the high resistance of both types of cells.

The early edema associated with inflammation must have a greater or lesser effect on the spread of infection. There would be a lessened flow of blood and lymph from the affected part and possibly other ionic or physiological changes having a bearing on the progress of the infection. The importance of leukocytes in such local reactions should not be underestimated, nor should the possible effect of other factors, such as local temperature change be overlooked.

The increasing use of local heat in chronic infections indicates the value of heat for such conditions. Taylor,[44] using a thermocouple arrangement on rabbits, found when heat was applied to the surface the temperature of the subcutaneous tissue rose to within 6° C. of the applied temperature, but with the needle 20 m.m. deep the highest rise was 1.5° C., at 42.5° C. on the surface.

The beginning of a bacterial invasion of the mucous membrane of the upper respiratory tract is evidenced in most instances by an inflammatory process. The inflammatory reaction is distinctly a protective phenomenon. Menkin[45] has shown a fine fibrin network in the tissue spaces and thrombosis of lymphatic in areas of inflammation. Foreign substances injected into the area did not readily extend to the regional lymphatics and when injected into the blood stream were fixed in the area of inflammation. Fixation occurred early, within 30 minutes, and was found to be due to mechanical blocking of the efferent pathways. The earliest sign of inflammation was found to be an increase in capillary permeability. Irritating substances are thus circumscribed and a period of time is allowed for the accumulation of phagocytes. The situation is well put by Opie,[46] who states that, "The vital organs are protected at the expense of local injury."

The rate of capillary filtration in inflammation was shown, by Landis,[47] to depend upon the difference between capillary pressure and the osmotic pressure of the plasma colloids. Inflammation of the mucosa may result in diffusion of fluids from the blood stream and conversion of a normally inert menstrum on the mucous surface into a good culture medium for bacteria.

6. *Natural Immunity.* Natural immunity should not be considered as a definite entity dependent upon fundamental individual variations but rather as being dependent upon the presence or absence of such factors as proper nutrition, metabolic fluctuations, fatigue, chilling,

or temporary physical depression. In some instances of endemic disease there may actually be an acquired hereditary resistance as a result of long adaptation of host to parasite. Natural immunity of the pigeon to pneumococci has been shown by Keyes[48] to be due to removal of the bacteria by Kupfer cells of the liver. Such resistance can often be broken down, as shown by Pasteur in the anthrax hen experiment, by drawing phagocytes away from the site of inoculation. Ordinary digestion in flat worms is carried on by means of phagocytic cells. Higher animals have converted the process into a mode of defense against foreign substances in the tissues and on the mucous surfaces. Great variations exist in the activity and efficiency of the phagocytic process under different conditions.

Natural immunity should not be confused with the effect of better economic conditions, and sanitation and hygiene, which may lead to a lessened exposure, and consequently a lessened incidence of disease.

Perfect functioning of the protective mechanism of the upper respiratory tract might well lead one to denote the condition as an individual natural immunity. The fact that the same individual may be exposed many times without contracting an infectious disease, and then suddenly come down with it, indicates the effect on resistance of fluctuations in internal and environmental conditions.

7. Local Immunity. The tissue cells and wandering cells of the body have been established as the ultimate source of resistance to bacterial invasion. It is well known that antibodies soon disappear from the blood stream in typhoid but immunity is lifelong. Why this should be has not been adequately explained but the more rapid response of tissue cells when again exposed is a factor.

Roemer found that by repeated application of abrin to the conjunctival sac of one eye, he could produce an immunity which first protected that eye, and then served to protect the opposite eye, in this later stage becoming a general immunity with antiabrin in the blood serum. Young[49] made repeated injections of electrolytes intrapleurally in rabbits. A single injection of 3/4 N strontium chloride caused hyperplasia of the epithelium of the marginal alveoli of the lungs, but a second injection, within 15-20 days, had no further effect. After a larger interval it became effective again. Hyperplasia did not occur, and finally no reaction resulted from the injection of 1 N strontium chloride, providing the concentration of the reagent was gradually increased in successive injections. The resistance was not strictly specific since calcium chloride provided some protection against strontium chloride. The resistance was readily broken by trauma or disintegration products of red blood

cells. It was a local resistance since it could not be induced by intraperitoneal or intravenous inoculation.

These observations indicate that a local resistance may be developed against both organic and inorganic substances. The local immunity, as in the case of the organic abrin, may result in an accessory generalized immunity through local absorption. There can be no doubt as to the existence of an acquired local resistance or immunity, just as there is an acquired local hypersensitivity, but the exact nature of the process and its relative importance in warding off infection is variable with the infecting organism and the tissue.

It is also true that certain organisms have a special affinity for certain tissues. Dysentery bacilli, or endotoxin, injected into the blood stream localize in the intestine and gall bladder. Besredka believes that local immunity to dysentery is the result of the development of a specific impermeability of the intestine. Many bacteria do not readily produce infection, except through a specific portal of entry, indicating a special adaptation of the micro-organism to the tissue. Besredka[50] states that intracutaneous immunization of guinea pigs against anthrax gives generalized protection although the blood does not possess protective properties. He believes that immunity in this disease is due to vaccination of the receptive cells in the skin.

Although no specific work is given relative to local immunity in the respiratory mucosa of the nose and pharynx there is no *a priori* reason why a special type of acquired resistance should not be present. Intimate contact with suspended matter in the air renders it a favorite site for local hypersensitivity. Several workers have produced immunity, active or passive, by making injections by the respiratory route. The respiratory mucosa is very extensive, fine and vascular, and absorbs with extreme avidity. Colin[51] states that Gohier put 30-40 litres of water into the trachea of the horse without producing death, and autopsy immediately after showed the water had been absorbed. Colin injected 18 litres into the trachea of the horse in three hours without considerable embarrassment. He recovered salts in the jugular vein four minutes after intratracheal injection. Drugs, anesthetics and soluble salts are taken up readily.

Pfenninger[52] compared the efficacy of intratracheal injection of bacteria with intravenous injection in the production of antibodies in the blood stream of rabbits. The intratracheal injection gave a lower agglutinin titre, but the injections were better tolerated, while precipitin and hemolysin production was at least as favorable as by the intravenous method. Bacteriolysins in the guinea pig were 4-5 times higher by intraperitoneal injection. A high degree of passive

immunity was transferred also. D'Aunoy[53] found antibodies produced in animals by intratracheal inoculation of various antigens. Agglutinins for B. dysenteriae and B. typhosus were as readily produced by this method as by the intravenous method. Lysins for human and sheep erythrocytes were elaborated more slowly, but bacteriolysins for V. cholera were found earlier, and in larger quantities, by the intratracheal route.

These observations emphasize the fact that on account of the rapid absorption from the respiratory mucosa a purely local immunity would be impossible to produce by ordinary methods.

The acquisition of resistance to pathogenic bacteria is likened by Besredka[50] to acquired tolerance to drugs. No doubt, in local immunity, chronic focal sepsis and drug resistance, some of the same factors came into play. It is necessary in order to get a true conception of the body and its reactions to various stimuli, to picture it as a physicochemical machine of a very complex nature. All reactions are chemical or physicochemical, taking place in a complex medium which varies with the tissue and pathological state, and influenced by physical and mechanical conditions.

DECREASED RESISTANCE TO BACTERIAL INVASION.

A general discussion has been given of the principal factors involved in the defense of the upper respiratory mucosa. The peculiar structure and location of this mucosa render it particularly susceptible to certain influences which tend to break down its resistance.

1. *Diet.* Food deficiency is unquestionably one of the most important predisposing factors to upper respiratory infection. Exposure or fatigue may appear as the precipitating cause but only because the membrane is already weakened from improper nourishment. With the membrane healthy, infection would not result until a critical degree of exposure is reached.

The destructive effect on the mucus secreting structures of the eye, larynx and trachea of the rat, resulting from a diet deficient in Vitamin A, has already been referred to (Mori[1]). The epithelium of the larynx was affected before that of trachea, with cornification of the columnar ciliated epithelium, which became thickened, and often infiltrated with pus cells.

Eusterman and Wilbur[92] state that many observers are agreed that Vitamin A is a physiological prophylactic against infection, by virtue of the fact that it maintains the integrity of the epithelial linings of the mucous tracts and the skin, but its "anti-infective" function is still

not established. They add, however, that accumulating experimental evidence tends to support the hypothesis that Vitamin A plays a part as an anti-infective agent.

Bloch[93] observed that scarcely two-thirds of the infants recovering from xerophthalmia reach the age of 8 years, but after this, their development goes on normally. He had many cases of severe infections in his 86 xerophthalmia patients. There was pneumonia and bronchitis in 27, otitis media in 13, pyelitis in 27 and pyoderma in 14. Children supplied with normal amounts of Vitamin A and those supplied with large amounts of this vitamin by Wright and Associates[94] failed to disclose any difference in the incidence of common colds in the two groups. McCarrison[95] has attributed the high incidence of infection of the nose and accessory sinuses to an inadequacy of Vitamin A in the diet.

Daniels, Armstrong and Dutton[54] found the first symptom of Vitamin A deficiency in rats was failure to gain, accompanied by loss of appetite, labored breathing and snuffles. Autopsy showed pus in the paranasal sinuses, mastoid cells, and frequently in the middle ear. They conclude from their findings that fat soluble A plays an important role in the immunity of the organism to pyogenic infections. Haladay[55] noticed that the nasal passages become involved and a characteristic respiratory infection usually appeared in the advanced stages of xerophthalmia. Cramer[56] found atrophy and necrosis of the intestinal villi in Vitamin A deficiency with degeneration of the mucus glands which were often filled with bacteria. He believes these changes, together with the increase in numbers of bacteria and parasites, explain the failure to grow. In a later publication Cramer[57] emphasizes the importance of milder degrees of vitamin deficiency and states that, "It is surely a suggestive fact that the two chief seats of disease in tropical countries, where the consumption of these articles of diet rich in Vitamin A is necessarily restricted, are the eyes and the intestines."

Cramer and Kingsbury[2] found positive blood cultures in four out of seven Vitamin A deficient rats. Staphylococcus aureus and albus, streptococcus and pneumococcus were found. Similar effects were produced by X-ray and radium. An increased susceptibility to lung infection was observed. The thrombopenia found in the later stages was explained as being due to bacterial invasion. Webster and Pritchett[58] found a slight delay in the death of mice fed on a diet containing sufficient Vitamin A, when injected with Bact. aertrycke, mercuric chloride or botulinus toxin. Topley, Greenwood and Wilson,[59] however, found that none of the substances added to a basic

diet of oats and milk gave added protection to mice against the epidemic spread of Bact. aertrycke infection.

Dean,[60] extending these observations clinically to children, found that best results were secured in treating sinusitis by combining a high Vitamin A diet with proper drainage.

Mendel[61] reports that Tyson and Smith find the principal changes in Vitamin A deficient rats to be metaplasia of cuboidal or columnar epithelium in certain parts of the body, epithelial hyperplasia in various structures, and infection. The metaplastic changes involve, in order, the sublingual glands, the submaxillary glands, and the epithelium of the renal pelvis, trachea and bronchi. The serous type of sublingual gland seemed to be the first affected. The usual condition in the trachea and bronchi was an atrophy of the lining cells while epithelial metaplasia was not common.

The possible relationship between Vitamin B and resistance has not been established. Sherman and Smith,[61] however, conclude that a pronounced deficiency in Vitamin B is followed by failure of appetite, decreased food consumption and finally starvation, gastric and intestinal atony, fall of body temperature and death. A moderate deficiency may lead to minor digestive disturbances and loss of stamina. Cowgill, Rosenberg and Rogoff,[62] making use of the fact that storage capacity of the body for Vitamin B is limited, found that forced exercise caused symptoms of Vitamin B deficiency to appear much earlier. They interpret this to mean that Vitamin B requirement is proportional to the metabolism of the tissue mass. Since loss of stamina is likely to lead to respiratory infection on exposure, these observations are of importance to otolaryngologists.

2. *Physiological Effects Causing Decreased Resistance. a.* Chilling There is no single factor of greater importance to the continued good health than proper temperature relationships. The development of acute respiratory infection following chilling is a matter of common observation. Severe exposure is quite likely to lead to pneumonia or acute upper respiratory disease. The resistance of different individuals is quite variable. An exposure sufficient to be quite dangerous to one person may be entirely harmless to one accustomed to rigorous climate. Just what constitutes such resistance has never been determined.

Mudd, Grant and Goldman[63] have shown that exposure of the skin to a draft of cold air results in ischemia of the mucous membrane, of the nose, pharynx and tonsils. This is followed after a short interval by hypermia which is greatest in the tonsil. Smiley[64, 65, 66] and coworkers have studied the effect of climatic and

seasonal influences on the common cold. Colds in Alabama were more severe than in Labrador, and those in Labrador much more severe than in a tropical island of the West Indies, where the temperature was quite constant the year round. These observations lead to the conclusion that the rigor of the climate is probably less important than its changeability in reducing resistance. This conclusion is supported by popular belief and the observation that respiratory infections are more common in the spring and fall when the weather is most changeable.

Smiley and Maughan[65] express the belief that the sudden change from 70° F., and 25 per cent humidity in the classroom, to 0° F. and 70 per cent humidity outside, is responsible for breaking down the resistance of cold susceptible students. The New York State Commission on Ventilation found such changes to result in a paling, swollen, nonresistant condition of the mucous membrane of the nose, as well as a decrease in the mobilization powers of the "immune bodies" in the blood stream. The incidence of common colds plotted monthly from 1912 to 1924 showed a definite reciprocal relationship with average temperature. Milam and Smiley[64] observed an outbreak of colds on an isolated tropical island coincident with a drop in minimum temperature below 74° F. Practically no colds occurred between June and November when the minimum temperature was above 74° F.

Townsend[67] observed outbreaks of common colds to occur simultaneously in widely scattered communities throughout the United States. Gafafer,[68] in studying the effect of weather conditions on upper respiratory disease in selected groups, observed, in the medical group studied, a slight tendency for the attack rate to rise during the period of October to April, when the temperature or vapor pressure fell below its ordinary level for the period. Results indicated that changes in weather in the warm season are probably more associated with upper respiratory incidence than changes in weather during the cold season.

Common observation suggests the existence of a hardening process due to constant exposure. A weather-beaten sailor would endure a great deal more exposure without ensuing respiratory infection than a person who has become thoroughly accustomed to indoor conditions. Whether this is due to decreased resistance as a result of the usual unfavorable atmospheric conditions indoors or to an actual hardening process under the more favorable outdoor conditions, or both, has not been definitely determined. It seems probable that the former is the most important factor. It is hard to see how exposure

beyond certain limits could ever be beneficial. However, a more stable vasomotor balance may be established as the result of repeated exposure of moderate degree so that extreme reaction does not occur when the exposure is more severe. That a vasomotor reflex from the skin to the nasal mucosa does occur was shown by the experiment of Mudd, Grant and Goldman.

b. Ventilation. A thorough discussion of this subject would involve a consideration of temperature, humidity, suspended matter and gases. Much has been written about ventilation but little done to determine the exact effect of these factors on the respiratory mucosa. Standards have been established by the New York Commission on Ventilation. They found that colds were less frequent in school children where the modified window method of ventilation was used. It is generally acknowledged that the humidity in our heated buildings is too low. Proetz[20] considers moisture as of secondary importance to ciliary action in maintaining the health of the respiratory mucosa. It is calculated that an average of approximately one liter of water per day is lost from the respiratory mucosa. This, of course, will cause a dehydrating effect inversely proportional to the relative humidity of the atmosphere since the expired air is always saturated. With sufficient fluid intake to maintain a healthy systemic condition and a normal mucus secreting function, it is difficult to see how a considerable range in atmospheric moisture could be a limiting factor in the health of the mucosa except in rare instances.

Suspended matter in the air is of great importance in special cases, such as specific allergy, or when laden with disease producing bacteria. Moderate amounts of inert matter probably do no harm.

c. Chemical Irritation. The presence of irritating gases or dusts, vomitus, and water from swimming may be considered under this heading. That these factors are of importance is evidenced by the presence of industrial diseases such as silicosis, authuacosis, "stone cutter's" tuberculosis, and the virulent type of tuberculosis resulting from prolonged inhalation of ammonia. The greater amount of damage in these cases is to the lower rather than the upper respiratory tract. However, Gray[15] showed that the ionic equilibrium of various cations has a marked effect on ciliary movement while the ordinary anions, cl, NO_3, Br, I, acetate, SO_4, tartrate and citrates have no direct effect, except as they interfere with the normal balance of cations present, but may interfere indirectly by causing disorganization of the tissue. Tartrates and citrates convert calcium to an unionized condition and OH ions reduce the H ion concentration. Ciliary

movement gradually slows and stops without calcium. Among the cations the rate of beat is least in Li, and greatest in K, with Na and NH_4 intermediate. The various anions were used in isotonic solutions of the sodium salt.

In view of these considerations and the relative importance of ciliary activity it is clear that ionic concentration on the mucosa may at times be such as to greatly reduce the defensive powers of the upper respiratory mucosa. The great damage done by concentrated solutions of acid, lye, etc., is well known but the minimum concentration of flue gases which may result in material damage to the mucosa has never been determined.

d. Metabolic Fluctuations. Such factors as fatigue, dissipation, overindulgence in food or alcohol and lack of exercise, as well as abnormal metabolic conditions due to internal secretions, are of undoubted importance in maintaining a high level of systemic resistance.

Zinnser[69] states that with fatigue or chilling there may be a temporary congestion of the mucous membrane, due to vasomotor influences, which interferes with the normal mobilization of leukocytes, permitting penetration of bacteria where they would ordinarily have been held back. Such an hypothesis furnishes an excellent physiologic basis for explaining the mechanism of all these metabolic factors in reducing resistance. However, the experimental results of Mudd, Goldman and Grant[8] in a study of the vasomotor reaction of the nasal cavity and postnasal space to chilling, indicates an ischemia rather than a congestion. In fatigue, ionic changes in the tissues, and alteration in mucous secretion may conceivably play a part. An ischemia in the mucosa in fatigue would correlate the observation of Zinnser; namely, an interference with leukocytic mobilization, with that of Mueller,[40] who found leukopenia resulting from peripheral vasoconstriction.

Overindulgence in food would also explain a mucosal leukopenia on the basis of Mueller's idea of a peripherosplanchnic balance in which peripheral vasoconstriction and leukopenia would result from a splanchnic congestion.

The relation of the internal secretions to the involuntary nervous system and metabolic rate may in a similar manner, in certain instances, account for a reduced leukocytic resistance and reduced mucous secretion in the upper respiratory tract. A lack of leukocytic response is always considered a danger sign and presupposes a more virulent type of infection.

e. Drainage obstruction, whether due to edema, tumor growth, or other mechanical factors, always predisposes to infection. Much

has been written on this subject so it will not be given further consideration here.

3. *Allergy.* It is a common observation to find infection associated with an allergic condition of the respiratory tract. In chronic sufferers it is unusual to find a case in which nasal operations have not been undertaken or suggested. There may be some question in individual cases as to the exact relationship of the allergy to the infection. Bray[71] in a very comprehensive review of the subject of allergy makes the following observations: *1.* An acute infection often ushers in the sensitive period, the dormant allergic state becoming active during the period of lowered resistance. *2.* In many cases, where hereditary history is absent, it appears that definite sensitivity develops to some allergen during the damaged state of the mucous membrane. *3.* An individual may be more susceptible to the inroads of infection, the micro-organisms thriving in the lowered resistance of a mucous membrane constantly irritated by specific protein. Thus it appears that either condition may be the primary one.

Proetz[72] observed that an apparently normal sinus membrane may increase in thickness to 1 c.m. or more within a few hours of a sudden asthmatic attack. This was considered as additional evidence against accepting nasal pathology as the cause of allergy. Gottlieb[73] found paranasal sinus disease in 26 per cent of 117 asthmatics, while Gill-Carey[74] found sinus abnormalities in 24 of 50 asthmatics, and approximately 30 out of 60 hay fever patients had sinus disease. Infection as shown by the presence of pus cells and pathogenic micro-organisms was found in nearly all cases regardless of hyperplastic changes in the sinuses. Bray[71] makes the further statement that the edema present during numerous repeated attacks of allergy finally produces hyperplasia of the lining mucosa of the various sinuses by interference with the blood supply and drainage. The ostia close and so the sinuses become fertile fields for bacterial invasion and growth. In these cases the reaction may be of a bacterial allergic nature.

The most common operation in allergic children is for tonsillar and adenoid hypertrophy and infection. However, sinus infection is rare in asthmatic children, and the purulent type of infection is rarely associated with asthma. The disease frequently follows winter colds or other infections prevalent at the time. Phillips[75] says that sensitization asthmas produce susceptibility to infection.

It is evident from these observations that infection has a double relationship to the allergic condition in the nose and throat. It may light up a dormant allergic diathesis and, secondly, it may be a com-

plicating factor in primary allergic conditions, the frequency of such complications increasing with the degree of chronicity.

4. *Trauma.* A considerable variety of factors may produce injury to the mucous membrane and are therefore frequently considered as traumatic in nature. These may all be considered under the headings of mechanical, thermal, chemical, and radiant or electrical injury. Although the body tends to react in the same manner to injury in all its parts, there are certain conditions peculiar to the nose and throat which make special consideration necessary.

Mechanical injury may be produced by a sharp instrument, or by a dull object, such as a septal spur or a foreign body. Nose and throat operations are surprisingly free of secondary infections, considering the amount of contamination. As previously mentioned, some authors, such as Fenton,[26] believe that trauma is a beneficial factor in operations on chronic sinuses, rather than a condition tending to deaden resistance. This may be explained on the basis of the local reaction which causes infiltration of wandering cells, hyperemia, etc., which may be just sufficient to upset the equilibrium between host and parasite. On the other hand, the general surgical rule of no operative procedure in the presence of an acute inflammatory process is just as important in nose and throat work as elsewhere and it is inconceivable that injury to a comparatively normal mucous membrane could accomplish any good.

The presence of dead tissue as the result of injury favors the growth and invasion of staphylococci and streptococci. Where a clean, incised wound would heal, a jagged wound might become infected. Tetanus is favored by the presence of dead tissue and staphylococci. Hence the value of the now widely practiced surgical procedure of debridement in lacerated and infected wounds.

Frankel, in 1895, noted the frequency with which acute lacunar tonsillitis follows trauma or inflammation of the mucous membrane. He believed the disease was primary in the mucous membrane. It has been noted that many bacteria may be introduced into the normal peritoneum without producing peritonitis, but in the presence of trauma, peritonitis results. Wherry[76] expresses the opinion that local edema produces food in solution for bacteria, dilutes antibodies, and prevents their entrance into the focus. He observes that bacteria which produce the most extensive local edema spread most rapidly through the tissues. Swelling is one of the cardinal signs of inflammation, whether produced by histamine-like substances, or by trauma.

The presence of a triangular calm area (Proetz[20]) in the nasal air currents on the floor of the nasal cavity posteriorly is a mechani-

cal factor of greatest importance. The deposition of dust, bacteria and foreign substances of all kinds would occur most readily at this point, just as silt is deposited in the calm portion of a river bed. Sore throats frequently start at this point.

Under chemical injury may properly be considered effects of toxins as well as pure chemicals, such as ammonia, arsenic and the amines; also the combined chemical and mechanical effects of swimming and vomiting.

The effect of toxic substances produced by bacteria may bring about cell death and aid in the invasion of the host. Bail discovered a substance in the peritoneal exudate of guinea pigs with tuberculous peritonitis, which caused death within 24 hours when injected, along with tubercle bacilli, into the peritoneal cavity of fresh guinea pigs. Controls receiving only the bacteria free exudate showed very little effect, and those receiving only tubercle bacilli died after several weeks. The substance was called "aggressin" but it was later shown by Wassermann and Citron,[77] and others, that substances with similar effect could be produced by extracting bacteria in vitro. According to Karsner and Ecker,[78] therefore, it seems probable that aggressins are nothing but endotoxins which have a negative chemotactic influence and nonspecific action. Ikomikoff found aggressins of Bact. coli, staphylococci and vibrios to act interchangeably. The influence of this factor in associative bacterial growth, so frequently found in chronic infections of the nose and throat, should be taken into consideration. It may account for the invasion in many instances by ordinarily avirulent bacteria.

Cl. septique, Cl. oedematiens and often Cl. tetani when completely freed of toxin by washing or heating do not produce the special disease when injected into rats or guinea pigs. The local tissue defenses are sufficient to rid the animal of bacteria in the absence of toxins, but if a small dose of ionizable calcium salt be injected, before, or at the same time as the toxin-free bacteria, the special disease results. The above observations may be very important in explaining why droplet infection is more effective in producing disease of the upper respiratory tract than indirect inoculation, where the accompanying toxic products may have been largely lost or destroyed. A diphtheritic infection is enhanced in virulence in the presence of a streptococcus or Vincent's infection. The growth of staphylococcus or streptococcus in wounds favors tetanus.

It may be pointed out that bacteria producing the most potent toxins are not the most active invaders of tissue. It has been noted[79] that a toxin which paralyzes the phagocytic and defensive cells is

most likely to convey high invasive power. Whooping cough, influenza and measles leave the individual in a very susceptible condition to secondary infection. These infections have the power of breaking down the local defense mechanism. The exact manner in which this takes place should be given further study.

The effect of cations and anions on the ciliated epithelium, and of calcium ions on general tissue resistance to certain infections have already been referred to. There is no doubt that inorganic ions in sufficient concentration are of great importance to resistance in the upper respiratory mucosa and in the general bodily defenses. Stark[80] found that irrigating the sinus of the rabbit, which is very similar to that of man as far as anatomy, physiology and histology are concerned, produced mucopurulent sinusitis in 62.5 per cent of those given 0.9 per cent Na cl, 80 per cent of those given tap water, and 82 per cent of those given 2 per cent Na cl. Controls showed no sinusitis. Continued breathing of ammonia fumes produces increased secretion of mucus and a chronic bronchitis.

Histamine produces marked contraction of smooth muscle, produces skin wheals, and in sufficient quantity produces shock. It is prevalent in body tissues but its action is limited to the immediate neighborhood of liberation. In the circulation it stimulates the secretion of adrenalin which neutralizes its action. Knott and Oriel[81] detected histamine-like substances in the sputum of asthmatics and others and conducted experiments which indicated their possible bacterial origin. Hanger[82] found that nasal secretions and saliva from humans and rabbits when injected subcutaneously into rabbits along with a virulent strain of B. lepisepticum, greatly enhanced the virulence of the bacterium. Secretions from acute colds accelerated the infection more, as a rule, than those from normal persons. The reaction was believed to be chemical in nature. Excoriation of the external nares in colds indicates the presence of some irritating substance in the secretions.

Mottram and Kingsbury[83] studied the effect of X-ray and radium emanations on the intestinal mucosa. Radium exposure was found to cause interference with production of mucus in the intestinal mucosa of animals, followed by necrosis. Blood cultures from irradiated animals were all positive for various bacteria. Similar results were produced by exposure to X-ray. There was not, however, a lowering of systemic resistance to bacterial invasion due to X-ray irradiation and therefore the occurrence of bacteria in the blood stream must be due to a breaking down of the local epithelial barrier.

The effects of thermal injury, except in relation to ciliary activity, have not been studied. All cilia show a minimum, optimum and maximum temperature for activity, which vary considerably with the origin of the cilia. Gray[15] found the effects of temperature on the frontal cilia of Mytilus were completely reversible between 0-28° C. Any rise above 28° C. caused individual cells to break away from the epithelium and when the temperature was reduced the activity was reduced. Effective activity did not increase from 34° C. up. The rate of beat began to fall at 37.5° C., the cilia came to rest in heat coma at 40° C., with heat rigor at 45° C., and irreversible injury at 47° C.

Properties of the Bacterium Affecting Its Invasiveness: The so-called virulence of a micro-organism is dependent upon the reciprocal relationship of the summation of the factors producing resistance in the host, and the invasiveness of the micro-organism. A decrease in invasiveness of the micro-organism causes a relative increase in resistance, and vice versa. A bacterium producing a severe epidemic among susceptible individuals may produce only mild symptoms, or no epidemic at all, among a relatively immune population. In the carrier condition, and in stationary chronic infections, an equilibrium exists. Most carriers, unless they be very temporary, have some lesion so that all but a very few could be called mild stationary chronic infections. Virulence, however, cannot be defined in terms of resistance. Most invasions of the body by micro-organisms are overcome.

If the course of such an invasion be followed, it will be observed that the first move is made by the micro-organism, which is countered by the host in a manner varying with the micro-organism and the portal of entry. The invader may then bring up reserves, consisting of micro-organisms which have been in lesser contact with the host defense. Here the time element is important and may determine the outcome. If the host reaction is sufficiently prompt and vigorous the infection is checked and usually the invader annihilated. Delayed response to the infective stimulus may be disastrous.

1. *Toxin Production.* The liberation of toxic products is one of the most important weapons of micro-organisms in their struggle to enter and penetrate the host tissues. This subject has already been discussed from the viewpoint of the host defense. The toxic substance may be a secretion, liberated by the living bacteria, a decomposition product of dead bacteria, or possibly a decomposition product of dead host tissues. Watson-Williams[84] in a discussion on focal sepsis points out the identity of the pathways of absorption of

toxins and of the invading micro-organism. The toxic substance paves the way for the invasion. Some of the true toxins, and possibly other toxic products, show a selective affinity for certain tissues. This may influence the direction of the invasion to some extent but the pathway of least resistance is likely to be the pathway of absorption also. Ordinary metastatic foci that lie in the tissues meet such a tissue resistance, that without continued reinforcement from the parent focus, they tend to resolve and disappear.

2. *Capsule Formation.* Capsule formation is another very important property of bacteria which enables them to resist the host defenses, such as the mucus layer protects the host against bacteria. Streptococci, pneumococci and anthrax bacilli are most virulent when encapsulated. Such bacteria are resistant to agglutination and phagocytosis but when the capsule is removed by treatment with acid they become susceptible to immune reactions. Capsule formation in many bacteria, like toxin production, takes place only under suitable conditions. The anthrax bacillus seldom has a capsule when grown on artificial media but in the diseased animal it is always encapsulated.

3. *Adaptability.* Adaptation of a micro-organism to its environment is probably the most important factor in establishing a chronic infection. Tolerance or resistance to unfavorable influences is rapidly developed by many bacteria. This has been shown repeatedly using biological and inorganic substances. The adaptation is brought about by survival and multiplication of the more resistant individuals, and, probably also, by some change in the individual micro-organism which enables it to better resist the deleterious substance. Gay and Claypole[85] found the typhoid carrier condition could be regularly produced in rabbits after cultivation of the bacillus in defibrinated rabbit's blood. Fleming[41] was able to produce lysozyme resistant strains of bacteria from susceptible strains by repeated exposure of the survivors in a culture. Resistance to immune reactions may be developed by continued contact with immune serum.

Danzsy[86] "immunized" anthrax bacilli against arsenic and found that resistant strains had developed capsules. The spirochetes of syphilis may become arsenic-fast when initial treatment is inadequate, thus rendering further treatment with this drug ineffective. The insusceptibility of the gametes of malaria to quinine is an example of variation in the effect of chemicals on different phases of the life cycle of the same micro-organism. Neuhaus[87] was able to develop a resistance of paramoecium to arsenic, antimony, copper and mercury. Numerous instances of development of tolerance of various bacteria to chemical substances are reviewed by Buchanan and Fulmer.[88]

Fluctuations in bacterial virulence, toxin production, etc., is one of the common problems with which the bacteriologist must contend in doing experimental work. The environment, both physical and chemical, organic and inorganic, ionized and nonionized is the all-important factor in determining the nature of the reactions between host and parasite. Bacteria act through the production of enzymes and the liberation of toxic products, which may be secreted, or freed by disintegration of dead bacteria or tissues.

4. *Ability to Lodge in Intercellular Spaces.* Invasiveness may take the form merely of ability to lodge in intercellular spaces (Zinner[69]). It is evident that a bacterium must be able to lodge or come to a more or less fixed position for a certain length of time before it can produce the initial lesion in a disease process. The required conditions, so far as known, are usually mechanical and are furnished by the effect of anatomical or environmental conditions upon the host. Menkin[45, 89, 90] has shown mechanical fixation of particulate substance and bacteria at the site of inflammation. Some factor other than the presence of bacteria seems to be necessary in order to produce brain abscess. In the upper respiratory tract factors such as viscosity, surface tension, and probably electrochemical phenomena, play a part in bringing about fixation of the bacteria. In some cases, when such lodgment occurs in the mucosa, the bacteria may be feebly exposed to the tissue defenses and continue to survive indefinitely in a sort of physiological incubator.

SUMMARY.

An attempt has been made to correlate the observations of various investigators and to show their application to the problems of the otolaryngologist in combating disease of the upper respiratory tract. In most instances, work has not progressed to a point where definite conclusions can be drawn. The principal object has been to bring the scattered and often fragmentary ideas together and in this way stimulate thought, and possibly greater activity, in this important field.

The problem is taken up from the standpoint of infection and resistance. The factors of importance in natural resistance of the upper respiratory mucosa to infection are mucus secretion, ciliary action, phagocytosis, lysozyme, local reaction, natural immunity and local immunity. The first three of these are by far the most important and the function of each is not only accessory to the others, but dependent upon them, for the full realization of its function.

It would not be correct to say that phagocytosis is the most important phenomenon in the defense of the mucosa, for certainly the other factors prevent all potential infections except a very occasional one. The mucociliary layer is marvelously efficient in its action and must be considered as the first line of defense, while phagocytosis and other factors, although showing some surface activity, constitute the second and third lines of defense.

Many influences tend to impair the natural resistance of the mucosa. The most important of these are: diet; physiological effects, including chilling, ventilation, chemical irritation, metabolic fluctuations and drainage obstruction; allergy; and trauma. All of these are important in the sense that any one may be the limiting factor in causing a break in the defense of the mucosa. It is impossible to separate local factors of decreased resistance from systemic factors, since the respiratory tract seems to be a favorite site for the manifestation of decreased systemic resistance. This may be due to the fact that it is more frequently exposed to potential infection.

There are certain properties of micro-organisms which affect their invasiveness. The most important of these are: the production of toxic products; capsule formation; adaptability to environment; and ability to lodge in intercellular spaces. That great variations in the virulence of many strains of bacteria occurs cannot be questioned. Even changes in type of pneumococci have been recently produced in vitro. All of the above properties of bacteria are probably quite variable and depend upon the particular environmental conditions. Toxic products may be considered as an extending arm for the bacterium which enables it to reach out far beyond its immediate environs. Capsule formation and adaptability, or development of tolerance to unfavorable conditions, are protective phenomena for the bacterium in its struggle against the host. Ability to lodge in intercellular spaces is a little understood phenomenon which must exist, however, in order for a bacterium to penetrate an apparently normal mucosa. It may be partly the result of properties of the bacterium and partly the result of changes in the host. Electrochemical and interfacial tension phenomena may be of importance in this connection.

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Scott and Euclid Avenues.

OTITIC INFECTION WITH GASTROENTERITIS IN INFANTS.*

Dr. Max Rabbiner, Brooklyn.

This paper represents a study of nine cases of mastoiditis in infants associated with gastrointestinal disturbances from the ear service of Dr. Marvin F. Jones at the New York Post-Graduate Hospital from April, 1928, to January, 1932, during which time 46 infants had been operated for mastoiditis. Of the nine infants who had both otitic disease and parenteral diarrhea, eight were operated upon, resulting in four recoveries and four deaths. The ninth infant was not operated upon, being considered a poor surgical risk by the pediatrists, and finally came to the autopsy table.

The relationship of otitic disease to gastroenteritis has aroused great interest among aurists and pediatricians as to whether the ear is a primary or secondary factor in the nutritional disturbance of infants.

Odoneal states that there are cases in which the malnutrition may be either primary or secondary to the infection, in the former as a result of the gastrointestinal disturbance, there is a lowered resistance which renders the infant more susceptible to upper respiratory infection which may involve the sinuses or ears, and in the latter the gastrointestinal disturbance is due to an infection of virulent strain of micro-organisms.

In a recent article, Maybaum, in making observations on cases of intestinal autointoxication in infants, was not able to establish any definite clinical entity between mastoid disease and the intestinal syndrome and where drums show abnormality before death and if mastoid infection is present, he recognizes it as a result and not the cause of the clinical picture of autointoxication.

Mariett, Lyman and others who have done considerable work in the field are of the impression that mastoid disease is an important etiologic factor in parenteral diarrhea in infants.

In our series of cases, the infants presented the usual history of failure to gain in weight in the mild type, while in the severest type continued vomiting, diarrhea, dehydration and marked loss of weight,

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associated with temperature varying from normal to 100°-101°-105°. They portrayed the usual sparrow-like appearance of the marasmic infant with a hopeless outlook.

With your indulgence I will briefly present the history of the following cases:

Case 65418: Patient, one month old, birth weight 7-2 pounds. Breast fed and gained for two weeks. Mother was sent to hospital and baby was put on formula. Baby began to lose weight. Admitted to hospital May 16, 1931.

May 16, 1931: A.D. drum membrane congested A.S. normal.

May 18: A.D. drum membrane red and bulging—myringotomy; serous fluid obtained.

Since pediatricians could not check diarrhea, considered same a case of parenteral diarrhea and suggested double mastoidectomy. Bilateral mastoidectomy under local; mucopurulent material in both antrums; pus in right mastoid and granulation tissue showing chronic purulent inflammation and abscess cavity. Left mastoid, necrotic exudate, two transfusions; discharged, improved, June 15, 1931.

Case 65015: Patient, 11 months old; birth weight, 5 pounds; weight on admission, 15-10. Admitted May 12, 1931. History of vomiting, 3-4 stools per day three weeks prior to admission.

May 14: A.D., D.M. retracted, good color. No fluid behind drum. A.S., extreme retraction with injection due to manipulation and loss of lustre. To be observed.

May 15. A.D. same. A.S., D.M. bulging, no landmarks, myringotomy, slight serous discharge.

May 18: A.D., same. A.S., D.M. resolving.

May 20: A.D., same. A.S., D.M. red and bulging, myringotomy pus obtained.

May 25: A.D., D:M. bulging in post. sup. portion, myringotomy, profuse purulent discharge and narrowing of canal. A.S., same. Advise bilateral mastoidectomy. Temperature, 100°-103°. May 20 and 26: General condition poor.

May 26: Transfusion.

May 27: Bilateral mastoidectomy, pus found in both mastoids, temperature normal in four days. General condition steadily improved.

Case 64976: Patient 11 months old. Birth weight 5 pounds. Admitted May 11, 15 pounds, with history of vomiting, cough for three weeks, chronically ill, marked rickets, normal temperature.

May 12: A.D., D.M. red and bulging, myringotomy, pus obtained. A.S., normal.

May 14: A.D., thick purulent discharge, rest of D.M. pink. A.S., small pustular area not ruptured in Shrapnell's area. Suggested bilateral mastoid because of history. Child did not do well and vomiting continued. Due to history of vomiting, etc., not controlled by feeding and for lack of other possible foci of infection. Right mastoidectomy was done May 16. No acute inflammation of mastoid was noted at operation, therefore left side was not done. Child continued to vomit and lose weight.

May 24: Definite signs of bronchopneumonia.

May 26: Child expired. Autopsy revealed bilateral mastoiditis, more marked on left side; septic meningitis, parenteral diarrhea and rickets.

Case 56359: Patient 8 months old. Birth weight, 5 pounds. Admitted Aug. 14, 1928, 8-8 pounds. Had diarrhea three weeks, age 6-7, bowel movements improved. Had another attack, Aug. 10, 2-4 bowel movements. Temperature, 99°-102°, double myringotomy in clinic, Aug. 10.

Aug. 16: Bilateral mastoidectomy, subacute mastoids, no free pus.

Sept. 3: Discharged, improved with abatement of G.I. symptoms.

Case 34990: Patient, 6 months old. Birth weight, 9½ pounds. Admitted May 12, 1928, 15-8 pounds; had been discharged two weeks ago with pneumonia, and three weeks prior to admission developed two discharging ears and have been discharging since with up and down temperature. Has diarrhea beginning one week ago.

May 16: A.D., right mastoiditis. A.S., ear resolved.

May 17: A.D., right mastoidectomy, granulation tissue, bleeding, hemorrhagic type, cyst of scalp opened, condition good for three days, but since then child continued losing weight; has diarrhea and continued abdominal distention. No response to treatment.

May 28: A.D., D.M. appears normal but due to history advise myringotomy, done. A.S., normal.

May 30: A.D., resolved all landmarks present. A.S., normal.

June 1: A.D., same. A.S., D.M. bulging, myringotomy, abundant thick yellow pus. Also advise mastoidectomy under local if pediatricians consent. No response from pediatricians.

June 6: Child expired. Autopsy refused.

Case 35105: Patient 9 months old. Birth weight, 11 pounds. Admitted May 19, 1928. Well up to six weeks ago vomited after meals, has continued to vomit after every feeding, lost weight, 3-4 watery stools, temperature, 102°.

May 20: A.D., D.M. bulging, opened, frank pus obtained. A.S., D.M. bulging, opened, frank pus obtained.

May 22: A.D., resolving. A.S., small amount of purulent discharge, appears to be resolving, no signs of mastoiditis.

May 28: A.D., resolving blood vessels injected. A.S., same. Treated with atropine and various diets; response was transitory, with periods of gaining and retention of foods; given clysis and transfusion, but did not improve. Pediatricians asked for bilateral mastoidectomy as prophylactic.

June 7: Bilateral mastoidectomy, local. Bilateral chronic mastoids, granulations, no free pus.

June 13: Expired. Autopsy, unresolved bronchopneumonia, chronic catarrhal entercolitis. No report of mastoids.

Case 35277: Patient 7 months old. Birth weight, 9½ pounds. Admitted May 24, 1928. History of two discharging ears since May 3, 1928. Temperature. 104° on admission.

May 26: A.D., signs of mastoid. A.S., signs of mastoid. Bilateral mastoidectomy done. Rt., suppuration with perforation through cortex. LT., chronic mastoiditis.

May 31: Began to lose weight because of diarrhea, transfusion. Prognosis as to ears favorable.

June 8: Patient shows no signs of meningeal involvement.

June 13: Stools watery, generally weak, transfusion given. X-ray of skull shows tendency to hydrocephalus.

June 15: Autopsy refused.

Cases 67351, 68357, 69055, 69844: Patient 4 months old. Birth weight, 4-14 pounds. Admitted Oct. 22, 1931. Admitted for regular treatment of laryngeal stenosis. Had been in three times previously.

Oct. 22: Laryngoscopy and treated for congenital deformity of laryngeal introitus; improved.

Oct. 22-28: During this time developed temperature, 103°-105°, and began to lose weight.

Oct. 28-Nov. 15: During this time vomited and developed diarrhea. Up to Dec. 22, ears examined regularly and found to be negative but vomiting and diarrhea continued.

Dec. 22: A.D., D.M. bulging, myringotomy, mucopus obtained, culture taken. A.S., D.M. bulging, myringotomy, mucopus obtained, culture taken. Following week the vomiting stopped but diarrhea continued, associated with loss of weight.

Dec. 31: A.D., D.M. bulging and prolapse of posterior canal wall. A.S., D.M. bulging and prolapse of posterior canal wall. Bilateral

mastoidectomy, local. Both mastoids filled with purulent material, and also necrosis in region of zygoma and antrum. Following operation, vomiting and diarrhea stopped.

March 1: Child had gained two pounds since discharge from hospital.

Case 71875: Patient 4 months old. Birth weight, 7-10 pounds. Admitted Jan. 11, 1932; weight, 8-14 pounds. Failed to gain in weight. Breast fed for 2½ weeks, mother thought her milk was not satisfactory. Put child on milk and water diet. At age of five weeks developed diarrhea, 5-6 stools daily; no cod liver oil given; examination showed marked rickets; X-ray, congenital heart. During the first two weeks at hospital weight curve was practically stationary on formula of milk, water and dextromaltose. T.P.R., normal and no vomiting.

Jan. 29, 1932: Eighteen days after admission to hospital developed temperature, 105°.

Jan. 26, 1932: A.D., dull, lustreless, prolapsed. A.S., dull, lustreless, prolapsed. Advised bilateral mastoidectomy if there is continued loss in weight.

Jan. 28, 1932: A.D., dull, lustreless. A.S., dull, lustreless. Redness in upper posterior quadrant. No bulging.

Jan. 29, 1932: A.D., dull and lustreless. A.S., dull and lustreless. Double myringotomy, small amount of serum obtained. Pharynx congested.

Jan. 30, 1932: Blood transfusion.

Jan. 31, 1932: Advised bilateral mastoidectomy. Pediatricians refused as child would not withstand operation.

Feb. 1, 1932: A.D., negative. A.S., negative (Dr. Smith). Crackling rales in right posterior and apex anterior. X-ray revealed low grade bronchopneumonia. Temperature continued for remaining four days and with it child vomited and lost weight gradually.

Feb. 6, 1932: Expired. Autopsy, acute congestion of brain, liver, spleen, pancreas, kidney and intestines. Left mastoiditis and otitis media; bronchopneumonia.

The otoscopic picture varied in this group of cases. In six, both drum heads showed bulging most often in the posterior superior quadrant and following incision a purulent discharge was obtained. Five of these six revealed either pus or granulation tissue in the mastoid antrum; in the sixth, the antrums were negative.

In the remaining three cases, the following observations were made: In one, both drum heads were not red but a dull, dirty gray,

with no definite bulge, and on myringotomy a few drops of serum was obtained. This patient was not operated on, as mentioned before, and autopsy revealed pus in the left mastoid. In the other two, the right ear was involved, from which on incision pus was obtained in one and serum in the other; in the latter a bilateral mastoidectomy was done and pus was found in both antrums, while in the former a right mastoidectomy revealed a negative antrum, but on autopsy the left mastoid was found to be filled with purulent material.

Both infants upon whom a unilateral mastoidectomy was performed expired.

The ages of these infants ranged from 31 days to 11 months. All were normal, full term deliveries. There were six males and three females. The birth weight had apparently no definite relationship as to the final outcome.

CONCLUSIONS.

From a study of the above cases it is apparent that those infants having otitic infection with parenteral diarrhea which cannot be checked by the pediatrists, mastoid surgery should be resorted to. The operation in all cases should be bilateral despite the fact that only one ear may show a definite otoscopic picture, while in the other the findings may be indefinite. Since the infection may be confined to the antrum and probably due to a localized pocketing of embryonal tissue around the aditus, the drum membrane does not show its true condition.

It is my impression that many of these infants have mild attacks of otitis media without symptoms which may or may not undergo complete resolution and act as a focus of infection. Although the intestinal history in each case antedated the ear condition, the latter probably is a definite etiological factor in this syndrome.

The often stressed point that co-operation between pediatrist and otologist is most essential for the proper study and care of infants who are suffering with this malady cannot be overemphasized.

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358 New York Avenue.

CORRECTION OF POSTAURICULAR DEFECT BY IMPLANTATION OF FASCIA LATA.*

DR. CHARLES M. GRIFFITH AND DR. ALBERT SCHATTNER,
New York.

Various plastic procedures are often required to correct abnormalities of the auricle and postauricular region. These are usually either congenital or the result of operation on the mastoid process. The congenital types are usually protruding ears or some form of microtia. Operations to correct these are fairly well standardized. The postoperative defects are in general fistulae or depressed scars. Many different methods have been used to repair these, with varying results.

The following case presents a problem that is rather unusual and is therefore reported.

A boy, age 14 years, was admitted to the Manhattan Eye, Ear and Throat Hospital under the care of Dr. Albert Schattner, for the correction of a deformity, which followed a mastoidectomy on March 27, 1931. Dr. Schattner did a secondary closure on April 4, 1931. Examination in March, 1932, showed a markedly depressed scar which had drawn the auricle in close contact with the head, producing a very asymmetrical appearance, sufficient to cause real embarrassment.

In order to correct this it would be necessary not only to free the adhesions between the superficial structures and the bone, but also to provide some support and padding to prevent reattachment and also to hold the auricle away from the head.

Knowing of the use of fascial transplants in other parts of the body, it occurred to us that it would be a suitable material for use here. On March 31, 1932, under ether anesthesia, a wide curved incision was made well posterior to the original scar and the periosteum elevated forward so as to free the entire area, which was found to be closely adherent to the bone, and in one place to the exposed lateral sinus. After this was completed, a section of the

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fascia lata, the size of the area elevated, was removed from the lateral area of the thigh, over the Vastus Externus muscle, and inserted into the previously prepared pocket, between the periosteum and bone.

The fat was retained on the fascia to add thickness to the graft. The wound was then completely closed with clips; no suture material was used as the graft does not require anchoring and the elimination of suture material probably lessens the chances of infection.

The wound healed promptly, with the result that you see.

Since we did this case, Dr. C. R. Straatsma and Dr. L. A. Peer have reported in the April number of the *Archives of Otolaryngology* the use of fat transplants in postauricular fistula with good results.

It would seem that this method, due to the ease with which it can be accomplished, together with the very slight inconvenience to the patient, would offer a very satisfactory method of correcting many of these unsightly deformities.

114 East 54th Street.

308 W. 48th Street.

A CASE OF RHINOPHYMA.*

Dr. H. Lyons Hunt, New York.

This condition, often simply designated as great hypertrophy of the nose, is probably only an aggravated type of gutta rosacea, or acne rosacea. As you can see from the photographs of the patient I present, several of the growths are sessile in character and the lowermost one is pedunculated.

While the case is by no means finished as far as surgical therapeusis goes, as a great deal of hypertrophied tissue must still be removed, I am showing him to you that you may note the result of the procedures practiced, and bring out the point that it is not necessary as a rule in these cases to practice skin-grafting after the growths have been removed.

These growths are extremely simple to take away. In this case our line of incision for each growth has been designed so that the skin covering the growth was itself largely saved, and dissected free from the deeper rhinophymatous tissue. The rhinophymatous tissue was then dissected down to the cartilage and the skin, although apparently involved, was used instead of newly grafted epithelium.

I have described several of these cases in my book on this subject and, like the cases so described, this case showed beginning fissures extending into the cartilage of the nose, although in this case the fissures did not extend through the cartilage. When fissures extend through the cartilage, the edges of the fissure must be freshened up and several sutures placed in the cartilage before the wound is closed. If subcuticular horsehair sutures are used in the closing of these wounds, and a salivary extract placed along the wound edge, little if any scarring results, and the case soon assumes a condition of normalcy.

412 West End Avenue.

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NASOPHARYNGEAL MALIGNANCY — CASE REPORT.*

Dr. E. H. Moyle, New York.

The patient is a 21-year-old Irish boy complaining of lumpy swellings in the neck, sore throat and difficulty and pain on opening mouth. He was admitted to the medical service, Jan. 2, 1932.

The first symptoms began in March, 1931, with typical attack of mumps, which subsided in three weeks. All the symptoms disappeared except the lumps in his neck, which grew larger.

Onset of trismus in June, 1931. He received nine X-ray treatments. A tentative diagnosis of tuberculous lymph glands was made. Chest X-rays at this time were negative for tuberculosis. Some decrease in the size of the neck glands followed the X-ray therapy, but began to increase about Dec. 1, 1932, associated with sore throat. An ear, nose and throat examination at this time revealed enlarged tonsils.

Physical examination on admission reveals inability to open mouth enough to make a satisfactory throat examination. The neck shows four distinct nodes in preauricular and anterior cervical chain on the right side. The nodes are hard, discrete, not attached to the skin, and non-tender. On the left side the swelling seems to push out sternomastoid in the preauricular region. Thyroid normal. A tentative diagnosis of Hodgkin's disease was made and lymphosarcoma or epithelioma suggested.

A biopsy of cervical gland on right side of neck was taken and reported: "Microscopic examination shows a lymph node in which, in several places, there are infiltrating collections of cells which are relatively very large, short spindle-shaped, or somewhat rounded, and which morphologically are indistinguishable from the so-called transitional epithelial cells encountered in certain varieties of plexiform epitheliomata." There are no histological evidences of Hodgkin's disease and the diagnosis of metastatic epithelioma is inevitable.

Postnasal examination with the nasopharyngoscope revealed the presence of a large mass which extended forward from the vault; had appearance of congested, enlarged, adenoid tissue. Biopsy was

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taken through the right side of the nose and the report was as follows: "Microscopic examination shows undifferentiated mass of epithelial cells having a plexiform arrangement. Scattered throughout this tissue are many mitotic figures. Diagnosis: Plexiform epithelioma."

One of the interesting features of this case (and of the last three similar cases examined) has been the presence of trismus practically from the onset. To my mind, trismus is a very definite indication of the presence of nasopharyngeal new-growth and a very careful search should be made in this area. (Examination with the postnasal mirror is practically never adequate in the presence of even the mildest trismus.)

In conclusion, let me say that the purpose in presenting this case report is not to enlighten this body of men gathered here tonight on the subject of malignancies of the nasopharynx. It is simply a plea for the more frequent use of the nasopharyngoscope and hence a more early diagnosis.

In my opinion, this instrument should be used routinely in every patient the otolaryngologist is requested to examine. We are criticized, and justly so, by the men working exclusively in cancer for not recognizing the presence of new-growths in the out-of-the-way recesses of the nose and nasopharynx until they are too far advanced for satisfactory treatment.

1088 Park Avenue.

RADIUM IN MALIGNANT TUMORS OF THE NASAL SINUSES.*

Dr. G. Allen Robinson, New York.

Malignant tumors of the nasal sinuses are rarely diagnosed early. Pain and severe hemorrhage are late symptoms in most cases. There are wide variations in the life history and extent of these growths. Likewise the histological types are many and varied. The etiology is not clear. Trauma, bad teeth, chronic sinusitis and polypoid degeneration of antral mucosa are causative factors. Malignant new growths in the nasal sinuses occur in young children as well as in adults. The clinical picture may be nasal obstruction, with or without ulceration and bleeding, prominence of one cheek, protuding eye, tearing, bulging hard palate and dull aching pains in the face. The patients are sometimes treated for many months for chronic sinusitis. The X-ray is of little value in the differential diagnosis. Infection and osteomyelitis accompany and aggravate the growth.

Biopsy of suspicious cases should be taken more often. Radical exploration of the nasal sinuses is justified in arriving at a diagnosis.

Radium and X-ray are valuable adjuncts to surgery or electrosurgery in the treatment of these cases.

The histological report of the tissue often determines the method of treatment. In the very cellular radio-sensitive types, as lymphosarcoma, lymph-epithelioma and schneiderian carcinoma, surgery may even be contra-indicated. In most cases, however, radium is applied in caustic doses to the tumor tissues at the time of operation and subsequently if the neoplastic tissue does not disappear. Proper drainage in these cases is imperative. The orbit is often invaded by infection or new growth, and enucleation of the eye or exenteration of the orbit becomes necessary.

I am indebted to Dr. A. J. Schwartz, Dental Surgeon, for his skill and patience in making the appliances that remedy the defects in cheek, palate and orbit.

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Good results have been obtained in the following cases:

Case 2225; Mrs. Rae R.; adenocarcinoma right antrum; referred by Dr. Harry Forbes; well for 14 years.

Case 2884; Clifford B.; fibrosarcoma right antrum; referred by Dr. Duncan MacPherson; well for 10 years.

Case 2334; William H. B.; lymphosarcoma right ethmoid; referred by Dr. John E. Mackenty; well for 7 years.

Case 2587; Margaret McG.; squamous-cell ca. right antrum; referred by Dr. Lester Hubby; well for 5 years.

Case 2588; Max B.; squamous-cell ca. right antrum; referred by Dr. Duncan MacPherson; well for 5 years.

Case 3262; David M.; schneiderian ca. left ethmoid; referred by Dr. Richard Moriarity; well for 2 years.

Case 3306; Tillie N.; papillary adeno-ca. right antrum; referred by Dr. Lobell; well for 2 years.

Case 3239; George K.; squamous-cell ca. right antrum; referred by Dr. Clarence H. Smith; well for 2 years.

Case 3374; Mabel H. H.; adenocarcinoma left antrum; referred by Dr. Ross Faulkner; well for 3 years.

Case 3342; Mary M.; fibrosarcoma right antrum; referred by Dr. Byron B. Kenyon; well for 2 years.

2 East 77th Street.

STYLOHYOID OSSIFICATION, BILATERAL, AND INJURY OF NINTH NERVE AFTER TONSILLECTOMY.*

Dr. Robert H. Fowler, New York.

In this brief paper two points in one patient are to be considered. First, an anomaly, stylohyoid ossification; second, the relationship of the ninth nerve to the tonsil operation.

In 1929, at 33 years of age, this patient had had twelve diathermy treatments for infected tonsils. Half a year later a member of this section operated on his throat and removed the tonsils surgically. The patient is now brought for consulation, saying there was more than the usual amount of difficulty at the time of operation and that, ever since then, the patient has had two symptoms, namely, constant and marked discomfort in the throat and an unpleasant taste.

The taste is salty, bitter and so bothersome that he has to take seven meals a day for temporary relief. The discomfort is so severe that he feels as if he were being *garotted*.

This quite unusual history leads up to a surprise when the examining finger receives a sensation on each side of the throat as though a firm wooden bar lay deep to the scar. On more careful palpation it is found that there is a slight give or flexibility at the lower extremity of the bar which runs forward and slightly inward to the very base of the tongue. This is pathognomonic of bilateral ossification of the stylohyoid.

X-ray photograph showed a slender bone running the whole length of the stylohyoid ligament with apparently a joint between it and the cornu of the hyoid bone. This anomaly had apparently existed since birth. Operative removal of part of the bone is contraindicated. The symptoms point rather to nerve trauma at the time of electric treatment or at time of tonsil operation.

This brings me to the second and more important matter. There has been in the last ten years a research undertaken at the anatomy

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department of the Western Reserve University with the object of making an accurate reconstruction of the tonsil and the anatomical structures closely related thereto. In the progress of this work there has been a growing suspicion that the ninth nerve in its normal course was vulnerable, separated as it is from the lower third of the tonsil by only a single thin sheet of muscle.

As you know, the upper lobe of the tonsil is in relation to thick bundles of both heads of the palatopharyngeus, reinforced by the superior constrictor shown in this plate. But the lower lobe has only a thin layer of the palatopharyngeus fibers adjacent to it. It is without reinforcement below the edge of the superior constrictor.

The exact point at which dissection goes wrong which will expose or injure the ninth nerve is a small fenestrum normally present half way down at the junction of the posterior and the lateral walls. Recently this point has been called the hilum by several authors, because it is where the main group of vessels reach the tonsil. The point is marked by the perforating bundle of stylopharyngeus fibers.

Fisher, of Cleveland, has seen what he designated as the ninth nerve exposed in the lower part of the tonsil fossa in no less than thirteen cases. He has even invented a technic of covering it in with muscle as though it were a hernia repair. And I have observed in a definite, though small, per cent of tonsil fossae after operation, perhaps one per cent, a structure which is apparently a nerve, not yet recognized or reported in the literature, closely connected with the ninth nerve, probably a branch rather than the nerve itself. This appears as a small white line. Exposure of this structure may occur because of removal of too much muscle with the tonsil, whether through poor technique or because of a scar; or, on the other hand, it may occur in the most meticulously careful dissection and be due to slight anomaly of nerve placement. Naturally, the more muscle removed the more apt it is to be exposed.

When this branch of the ninth is seen on one side of the throat it is apt to be seen also on the other side, showing that it is related to the anatomical variation. It is very frail, is easily broken and is difficult to identify, for it resembles a vein or a strip of fascia.

Will Rogers says: "It ain't *how much* you see that counts, it's *knowing what* you see when you see it."

So much for the findings within the tonsil fossa. The normal course of the ninth runs between the lower third of the tonsil and the stylohyoid muscle. Now if the stylohyoid ligament were metamorphosed into bone it would be logical to expect injury to the

ninth nerve after tonsil diathermy and surgical removal. In a case like the one we are studying, how could the ninth nerve escape?

But to get further evidence I have asked Dr. Krogman, in Todd's anatomical laboratory at Western Reserve University, to look up the relationship of the ninth nerve in the case of stylohyoid ossification reported by Dr. George Leonhart. He writes: "I could not pick up the ninth nerve on the left side, but on the right side it was clearly demonstrated. After coming through the jugular foramen it passed down and slightly forward medial to the internal carotid artery for about an inch. It then turned slightly forward to lie upon the stylopharyngeus muscle, *underneath*, i.e., *medial* to, the ossified stylohyoid. About three-fourths of an inch from the end of the greater horn of the hyoid it entered the substance of the pharyngeal wall just over, that is, external to the tonsil. It is worthy of mention that on both sides the vagus, the internal jugular, the carotid, and the muscular relationships did not depart from the normal.

"As regards the specific instance mentioned by you it seems entirely probable that the tonsillectomy may have involved, slightly, the ninth nerve quite independently of the ossified stylohyoid. What I mean is this: that variation in the glossopharyngeal nerve so that it is very close to the tonsil may occur apart from the anomalous classification."

Parallel to the increase in our information about the proximity of the ninth nerve and the tonsil has grown the suspicion that certain symptoms following tonsil operation, symptoms and physical signs are caused by injury to this nerve.

Dr. Irving Pardee, the neurologist, has consented to discuss this, and he will give us the clue to the solution of this particular patient's problem.

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153 East 62nd Street.

TONSILLECTOMY IN THE PRESENCE OF THYROID DISEASE.*

DR. H. G. BULLWINKEL, New York.

A great many papers presented at medical meetings deal with the more unusual and bizarre conditions met with in medical and surgical practice. It is the purpose of the writer of this paper to present a fairly common condition which is met with not infrequently and which at times is given too little thought, namely: tonsillectomy in the presence of thyroid disease.

We are all aware of the fact that infection of the nasopharynx may be an etiological factor in thyroid pathology. In fact, the writer just recently in private practice had a patient who presented himself with sudden and considerable enlargement of the thyroid which was limited to the isthmus alone. This was coincidental with a moderately severe pansinusitis. The patient's attention, however, was drawn to the thyroid enlargement and he was more concerned with it than he was with the infection in the nose and sinuses. Needless to say, within a few days after treatment was given the sinuses, the thyroid condition subsided.

Those of us who have done much tonsil work have seen many times thyroid pathology of different types improved after the removal of the tonsils. The writer has personally questioned many of the outstanding laryngologists in this city and they have all felt that tonsillectomy is, by and large, indicated in thyroid disease.

Crile, in his volume on the "Thyroid Gland," states that it is usually advisable to remove the tonsils along with other foci of infection before thyroid surgery is undertaken.

The writer has always concurred in this belief until two cases on whom he performed tonsillectomies developed subsequently thereto an acute thyroiditis. Only this winter a case was reported at the New York Polyclinic Hospital of an acute thyroiditis following electro-coagulation of the tonsils. In a personal communication

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with the writer, Dr. Luther MacKenzie of Bellevue Hospital, reports a fatal case of acute thyroiditis following tonsillectomy.

Case 1: F. E., female, age 22 years. Patient was referred to me for tonsillectomy and gave a history of having had frequent attacks of acute tonsillitis and about six months previously a severe peritonsillar abscess.

Upon examination the tonsils appeared to be definitely diseased. Her entire physical examination was negative, except for the presence of a slightly enlarged thyroid gland. This was felt to be what is often called an adolescent type of goitre. Her pulse rate was 68, her metabolism 14, and she was at least 40 pounds over-weight. Clinically, she appeared to be more of the cretin rather than the hyperthyroid type.

A tonsillectomy was performed at 2 p. m., and was quickly and easily carried out. After the patient reacted from the anesthesia a quarter of a grain of morphine was given. This seemed to excite her, but when three and a half or four hours had elapsed another quarter was given. This also excited her rather than acting as a sedative.

She had an extremely nervous night and the nurse called me in to see her around 7 a. m., when I found, greatly to my surprise, that her thyroid gland had increased two or three times its previous size. She had also developed some exophthalmos and all of the signs and symptoms of thyrotoxicosis. This condition persisted throughout her convalescence, though it abated somewhat in its intensity.

She was taken to Roosevelt Hospital, where several metabolism tests were taken which ranged from +50 to +60. After prolonged study a subtotal thyroidectomy was performed by Dr. Henry Cave. The patient today is well and has since become the mother of two children.

The second case I have to report is a sister of Case 1—(E. W.).

She was of a decidedly different type, having clinical signs and symptoms of hyperthyroidism with a metabolism of +30. She had had several attacks of acute tonsillitis and with each of these attacks the symptoms of thyroidtoxicity increased.

She was advised to have her tonsils out by her own physician. Before removing them, however, I had her confined in the hospital about a week for observation and rest. Having had a disagreeable experience with her sister, as reported above, I sought and received

the advice of several other laryngologists. They all felt that the removal of her tonsils was indicated and that undoubtedly her thyroid condition would improve thereafter.

Her metabolism having dropped to +18, I removed her tonsils. She developed the same reaction that her sister did, though not to as alarming a degree. She eventually recovered though she still has mild symptoms of hyperthyroidism. She was living in the west when I last heard from her and is apparently greatly improved.

I am not reporting these cases to prove or disprove any stated theories, simply as a warning to all of us to be aware of this condition when we meet it.

My own opinion is that, by and large, attention should be given to the thyroid disease first and to the tonsils second, for it is certainly possible to precipitate an acute thyroid crisis by surgical procedures unless extreme care and thought is used.

30 East 76th Street.

EXTRINSIC LIPOMA OF LARYNX.

Dr. James A. Flynn, Washington, D. C.

The periglottis is that small triangular space situated between the thyrohyoid membrane and the thyroepiglottideous muscle and above the hyoepiglottidean ligament. Therefore, it is posterior to the body of the hyoid bone and anterior to the root of the epiglottis. Normally this space is filled with a small amount of fat, but when the fat assumes abnormal proportions and interferes with function it becomes pathologic and is called a lipoma.

A lipoma is a tumor which is composed of adipose tissue and belongs to the connective tissue group. When fat and mucous tissue grow together we term the tumor lipo-myxoma, and when there is a large amount of fibrous tissue it is called lipo-fibroma.

These tumors do not metastacise, but many may appear at one time throughout the body. Calcification, gangrene, necrosis and sloughing may occur in lipomas.

Curiously, a complete disappearance of lipoma does not occur, even when the patient undergoes marked loss of flesh, as in phthisis.

Lipomas have been observed in the new-born, and the favorite sites of appearance are the tissues of the back, neck, axilla, abdomen and thighs. Among the ancients such enlargements were considered a mark of beauty. Shattock, in a comprehensive article in the Proceeding of the Royal Society of Medicine, discusses the beautiful buttocks of the Hottentot women and ancient Egyptian women. Many photographs of clay figures and sculptures illustrate his article and demonstrate the importance attached to these tumor formations by these people.

A rare condition which occurs in man is the new growth of fat in the neck and throat. I will describe such a case. Certain tissues of the body contain under normal conditions a considerable amount of fat, which is present in the cells in such amounts as to be readily recognizable by the naked eye. This fat has its origin in the fat ingested with the food or has been formed in the body from albumin and carbohydrates and has been deposited in the tissue in which it is found. When the ingestion of fat or fat-forming substance is

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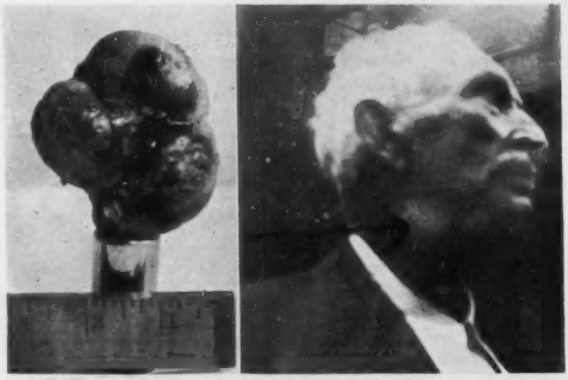
abnormally great, or the body is unable to make proper use of the fat consumed or elaborated in it, a disturbance of the balance of fat production and fat consumption results, leading to an increase in the storage of fat in the body. In time this interferes with the performance or function by the tissues and these become of pathologic importance. Fat may be removed from the cells by a process termed serous atrophy or pigment atrophy. Fatty degeneration may occur in the course of a parenchymatous degeneration. It is really a splitting up of the protoplasm of the cells with fat formation. Many organs of the body show such changes, especially the liver and heart.



Lipoma removed from C. W. P. Weight 114 grams.

Fatty degeneration is thought to be due to a change in the composition of the blood. There seems to be a persistent diminution in the supply of oxygen to the cells and therefore fatty degeneration frequently accompanies conditions producing general or local anemia. Blindness following serious loss of blood has occurred, the blindness being due to fatty degeneration of the retinal cells or to the optic nerve in the region of the lamina cribrosa. Various poisons may bring about increased degeneration of albumin and consequent fatty degenerations. A peculiarity about fat contained in lipoma is that it generally persists although the fat of the body is absorbed.

Weber records a case of lipoma of the neck, arms, and pubic region that persisted although the patient suffered an enormous loss of weight.

Shattock cites several cases of lipoma which persisted although the patients lost weight due to phthisis.

Goldstein, in an excellent article in THE LARYNGOSCOPE, reports a case of lipoma of the larynx and a comprehensive revue of twelve cases of laryngeal lipoma. He says that lipoma of this region is infrequently found or reported.

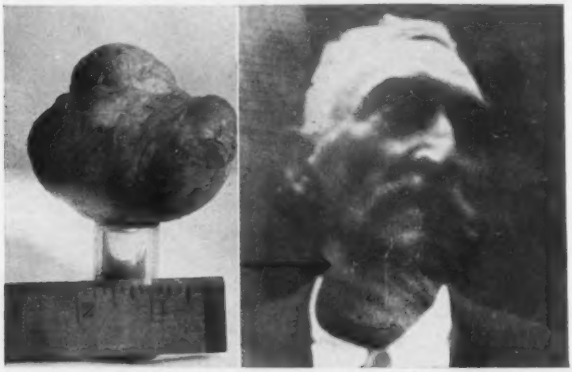
The case I am reporting has many interesting phases.

First, its large size and slow development are conspicuous.

The patient, Mr. C. W. Price, age 64, native of Maryland, occupation, fisherman, was examined during December, 1925. He was a large, healthy appearing man. He complained of pain in his neck and throat, and dysphagia. Articulate speech was very poor and it was with great difficulty that I was able to understand him.

Family history negative.

Previous history: Usual diseases of childhood. No illness until 10 years ago, when present trouble began to manifest itself. He began to have discomfort and sensation of fullness in his throat, dysphagia, and frequent coughing spells.



Lipoma removed from C. W. P. Weight 114 grams.

He was then treated for asthma with negative results. His dentist told him that there was something wrong with his throat. His condition became steadily worse. He visited specialists in Baltimore, Philadelphia and Washington.

During my examination in December, 1925, I found a large, smooth tumor mass at the base of his tongue; it pushed back his epiglottis, thus producing dyspnoia and his inarticulate speech.

Several lipomatous tumors were found on his body. Operation for removal was recommended and accepted.

I injected novocaine 1 per cent into the capsule. Then an incision was made into the capsule and the tumor was dissected free. It was a pure mass of adipose tissue, weighing 54 grams. This removal gave considerable relief and the patient was able to articulate better and able to take food without trouble. He said that he was perfectly satisfied.

I saw no more of the patient until 1931, when he returned with a recurrence of the tumor. The tumor now seemed to be growing more to the right side of his neck and was quite conspicuous just in front of the sternocleidomastoid muscles and toward the hyoid bone. But because no dyspnoia nor dysphagia existed, I advised waiting until the growth became more evident on the external surface of the neck. This the patient agreed to do. He returned again in May, 1932. The tumor was at this time very large. On palpation it seemed about the size of a small orange.

On May 28, I removed the tumor mass by external incision, beginning at the sternomastoid muscle and extending across the neck to the hyoid bone. The enucleation was easy and practically bloodless, the facial vein requiring ligation. This tumer weighed 114 grams. It seemed to spring from the periglottic space and burrow out into the neck along the body of hyoid bone and the thyroid cartilage toward the median line and over to the great vessels of the neck laterally.

Microscopically the mass was adipose tissue with connective tissue septu.

Articulate speech is now possible, although there has recurred a small lobulated mass at the base of the tongue, at the site of the tumor removed in 1925.

The accompanying photographs show the tumor in the neck and the photographs of the specimen give some idea of the size of this lipomatous mass.

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1511 Rhode Island Ave., N.-W.

A CASE OF LARYNGECTOMY, FOURTEEN YEARS AGO.*

Dr. John McCoy, New York.

This case of laryngectomy was seen by me in my clinic at the New York Eye and Ear Hospital on March 5, 1918. At that time he gave a history of progressive hoarseness of four months. Examination of the larynx revealed infiltration of the left vocal cord, false cord, arytenoid and interarytenoid space extended over to right side. In the center of the infiltration was the typical cauliflower appearance of carcinoma. Two large hard glands could be palpated under sternomastoid on the left side at the level of the hyoid bone.

A Wassermann was obtained by his physician proved negative. His teeth were in bad condition from pyrorrhea, his nasal accessory sinuses were normal.

He was referred to the dentist, who treated his mouth for one week and thoroughly sterilized it.

Meantime his tonsils were having treatment by means of suction and silver.

On March 19, we began with his laryngectomy. The indications for this operation are extrinsic cancer. Infiltrating one or both sides of the larynx above the glottis, the technique adopted by the writer in operating these cases is as follows:

When a tentative diagnosis of malignancy has been made we first order a Wassermann blood test to be made, the patient is also referred to a competent dentist for thorough cleansing of the teeth, the removal of decayed roots and thorough removal of pyorrhea and pus cavities. Nasal condition is also examined and the accessory sinus investigated, also tonsils have suction and silver every other day. The patient is then ready for the removal of a section, from the growth for microscopical examination. If the diagnosis is at this time practically unquestioned in the mind of the operator, a preliminary low tracheotomy is performed just before or after the section is taken. The patient is then put to bed in a room in which

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a croup kettle is moistening the air. Mouth and teeth are sprayed with alcohol solution and argyrol solution, and at the end of the first week, during which we have received the pathological report, we are ready to proceed with the extirpation of the larynx.

An incision is made from the hyoid bone to within one-half inch of the preceding tracheotomy incision. The thyroid and cricoid cartilages are exposed and after the thyrohyoid and sternothyroid muscles are severed, their attachment to the thyroid cartilage, the thyrohyoid and cricothyroid membranes are freely exposed, the tissue in the neighborhood of the superlaryngeal nerve and also the thyrohyoid and cricothyroid membranes are infiltrated with weak novocain solution, the dissection is then continued down the sides of the thyroid and cricoid until we reach the esophagus. A horizontal incision is then made, severing the cricoid cartilage from the first ring of the trachea, a tenaculum is placed within the cricoid. It is pulled forward and its posterier aspect is dissected away from the esophagus up to the arytenoid cartilages. With an incision directly across the thyroid membrane and all the way through it, we now detach the larynx completely. The opening into the lower pharynx is now sutured together without perforating the mucus surfaces and the tissues over this are sewed together by blanket sutures. The trachea is dissected free for one or two rings and stitched forward to the skin of the neck by heavy sutures, a skin flap also being thrown around and sutured to the back of it.

This is the operation the writer has done ever since with excellent results.

730 Fifth Avenue.

THE NEW YORK ACADEMY OF MEDICINE.

SECTION OF OTO-LARYNGOLOGY.

Meeting of Dec. 21, 1932.

(Continued from March issue, THE LARYNGOSCOPE.*)*

We should be honest with ourselves first, and then with our fellow physicians regarding any rash statements which will in the end discredit us, not only in the minds of the laity, but also with the medical profession.

As mentioned in the third paragraph, we do have complications in our tonsillectomies at Manhattan Eye, Ear and Throat Hospital, and I doubt if any of those present will live to see the day of a perfect tonsillectomy, as each patient presents a different problem for us to solve.

I have seen nearly all of the patients treated by Dr. Jasper and Dr. Hubert, and those shown at the meeting of the New York Society of Physical Therapy in December, 1930, in the Academy, and will agree with the conclusions of Dr. Yonker and Dr. Dougherty from Dr. Shambaugh's Clinic, namely, that they had never seen a tonsil fossa free from tonsil tissue.

In conclusion, will say that there may be four indications for the use of this method as having a somewhat scientific basis: (1) Tonsillar stumps. (2) Diseased tonsils in tuberculosis with reservations. All observers are generally agreed that it is inadvisable to perform a tonsillectomy on a patient suffering with far advanced, active or progressive tuberculosis, and there is considerable difference of opinion whether the operation is contraindicated in the earlier and milder forms. Electrocoagulation has not been used on enough tubercular patients to give accurate reports. (3) Hemophiliacs, as stated earlier in this discussion. (4) Hypertrophied lingual tonsils or lymphoid tissue in the posterior pharynx.

Nearly all writers list under indications the group who refuse to have their tonsils removed surgically, but who should be classed under influencing circumstances.

DR. HENRY HALL FORBES: In continuing the discussion I may also remark that I, too, have prepared my part of it, and with Dr. Jones' permission I will also suggest that while Dr. Jones' observations have undoubtedly required, as he says, some time and thought to prepare, I would have been more pleased if he had been able to give his personal experience. No one questions the excellent work at the Manhattan Hospital, and when those using surgical diathermy in selected cases have a total of 35,000, I am quite confident we will have perhaps another report to make.

I am grateful for the opportunity of participating in the discussion of this most scientific and well presented contribution covering, as it does fully, the use of surgical diathermy in diseases of the ear, nose, and throat. I also congratulate Dr. Imperatori on his wisdom in selecting Dr. Hurd to present this timely subject. His work—most exhaustive—has been presented to us in a thoroughly up to date and comprehensive form. It is most pleasing to have him give us this practical demonstration of his experience in both a teaching hospital and in his private practice. His demonstration, with the assistance of our fellow member, Dr. Morrison, at the Polyclinic Hospital this afternoon, was most interesting and instructive. From experience I know of the time and thought one must give to a demonstration of this type of instruction. As I must from now on but voice the positive statement of Dr. Hurd, this might be an opportune time for me to sit down, but I am so interested in the subject that I hope you will bear with me for a few moments that I may give you my reaction to the use of surgical diathermy in our specialty.

Every member of the New York Academy of Medicine is interested in any and all methods of treatment which will benefit the patient and advance the science of medicine and surgery. I say this, having in mind the criticism of those who have been critical when the use of electricity has been advocated. We all recognize Dr. Hurd's standing in the field of otolaryngology; perhaps this, plus the work of many other members of our section, may give the necessary stimulus to many who have been doubting the actual value of this method of treatment. That it will destroy lymphoid tissue and that it has a place in our field of work has been demonstrated when used by those already trained in the surgery of our specialty and have been able to make a study of the instruments and their control; and, further, that it is a scientific, efficient, and established method of dealing with selected cases as they occur in the field of otolaryngology. To attack lymphoid tissue in both the nose and throat by means other than cutting is familiar to us all. $AGNO_3$, chromic acid, have had their day; the use of the galvano-cautery goes back, to my personal knowledge (and before), some forty-five years, when the late Dr. Knight, one of our older members, used that method to shrink the inferior turbinates. These new terms, fulguration, surgical and medical diathermy, electro-coagulation, unipolar and bipolar methods, are the ones used in describing this new "Electro-Surgery." New improvements in machines and technique are sure to come.

The applicator I was to present, Mr. Chairman, I believe to be one of the original as used by my former associate, Dr. Finlay Cook, in 1906, when Dr. Cook and I began the use of fulguration for the destruction of diseased tonsils—very slow work, I assure you. We also used this method in the nose to control cases of septal hemorrhage; I am not sure that I used it on turbinates, but I did use the method with Dr. Harris at the New York Post-Graduate Hospital in several cases of papilloma of the larynx and fauces.

Dr. Hurd, I am sure, has the full endorsement of all those who have used surgical diathermy in their practice. I feel warranted in continuing the use of this addition to my means of treating certain selected cases. The work as already established by no means replaces surgery, but must be acknowledged as of value in otolaryngology.

Dr. Wallace Morrison: May I stress one point that has not been brought out as forcibly as its importance warrants? This is in reference to the proper course to be followed by the many men who know little or nothing of diathermy, but who are interested and wish to begin the use of this very useful method of treatment.

There are several very definite essentials, and the approach to the subject must be that of the student. First of all, one must have a knowledge of the physics of the types of currents to be used, and of the physiology of their effects when applied in various ways to the human body. These facts are set forth in any one of several recent textbooks on the subject; acquaintance with one of these is the first essential. Constant touch with both the standard journals publishing articles on diathermy by reputable writers, and contact with men now doing the type of work you are most interested in, are other necessary parts of one's study.

Having access to a really modern diathermy generator, one must provide himself with properly made electrodes and applicators necessary for the type of work to be performed. Then he must spend considerable time on patient experimentation with every type of current he proposes to use, and every sort of manner of applying the current, working on fresh meat, until he is thoroughly informed as to the details of the control of his diathermy machine, and the actions of its currents. Then, and only then, should he attempt the actual treatment of patients, and under the guidance of someone who had had experience in this special work.

Dr. M. M. Jasper: First, I wish to thank the officers and members of the Section for the opportunity of relating my experience with and expressing my humble opinion upon the highly publicised and much advertised subject of diathermy in nose and throat work, and more especially as it relates to the removal of tonsils and adenoids.

In about eighteen months of conscientious effort and ample facilities, I have not been able to substantiate the numerous advantages claimed for this method as contrasted with the alleged horrors and dangers of orthodox surgery. Most of the claims advanced by the diathermy advocates are exaggerated, while others are fantastic to the point of incredibility.

Claim 1. Painlessness: This must be taken with a grain of salt, or rather, anodyne. Any agent which destroys living tissue may and sometimes does produce pain.

Claim 2. Bloodlessness: Not only is this claim at variance with my experience, but is contradicted by the statistical table embodied in a reprint published by one of the advocates himself. I have seen several cases of mild bleeding and two cases of alarming hemorrhage. One of these, a dentist, came to me immediately after his initial treatment and bled so freely that an emergency tonsillectomy was seriously considered in order to stop the loss of blood.

Claim 3. Quotation: "Diathermy is suitable for the removal of all kinds of tonsils in all cases." Young children are swept into this broad inclusion. One man cites the case of a child six years old whose tonsils and adenoids were successfully removed under topical anesthesia in fourteen treatments. I must confess that this report puts a severe test upon my credulity. Even adults are not always suitable for this treatment. Some gag so readily that the delicate manipulation demanded by the electric needle becomes almost impossible; in others, the tonsil tissue is so resistant to coagulation that their complete removal becomes a very discouraging task.

The so-called aponeurosis of the constrictor muscles supposedly lining a clean fossa after the final diathermy treatment, upon searching examination turns out to be a layer of smooth scar tissue, frequently superimposed upon remnants of tonsil tissue. These tonsil remnants are not sterilized by the diathermy treatments, as claimed, and I have seen them acutely inflamed and exuding pus on pressure. It is, of course, conceivable that tonsil remnants after any instrumentation may remain free from infection, but this is a coincidence and not a principle.

There appears to be a lack of unanimity among the diathermy advocates as to the modus operandi. One gentleman, after coagulating the entire tonsil surface to the point of blanching completes the seance by fulguration. Another one insists that fulguration leaves scar tissue and very unsatisfactory results. There is, however, complete unanimity as to the perfection of the results obtained. Not only do they contradict one another on vital points, but they contradict themselves.

One gentleman, on page one of his reprinted article, states: "Modern medicine emphatically supports the principle of eradicating all foci of infection." On page six of the same article, he asserts that: "Many persons are aided by mere destruction of the active infection in the tonsils, and actually do not require complete eradication." How he differentiates the actively infected portion from the remainder of the tonsil, he fails to explain.

Another writer, after extolling the virtues of diathermy—freedom from pain, freedom from hemorrhage, security against all complications—has this paradoxical admonition to offer: "If you want every afternoon for golf, do not take up diathermy."

I could not do better than to refer to the conclusions of Drs. Yonker and Dougherty of Dr. Shambaugh's clinic in Chicago, published in the Surgical Clinics of North America, October, 1932: "Diathermy is useful in reducing the size of relaxed, turgescent turbinates; it is useless in polyps, and dangerous in adenoids. It is useful but not indispensable in removing lymphoid hypertrophies on the posterior wall of the oropharynx." They were very much disappointed in the application of this method in the removal of enlarged tonsils, "because it is too costly in loss of time to the patient; the discomfort to which he is subjected is much greater when one considers the number of treatments required; the method is not free from danger of secondary hemorrhage, and when such occurs the friable condition of the treated area renders the control of the bleeding more difficult."

The end results in efforts to remove tonsils by electrocoagulation are very discouraging. In spite of prolonged and patient efforts they have yet to see

a single case free from all lymphoid tissue in the tonsil fossae. The claim that the tonsil remnants are harmless, they brand as preposterous.

In conclusion, they emphatically condemn the ill-advised exploitations of diathermy through misleading statements in health columns of the daily press and through notoriety seekers in the medical profession. In this condemnation, I heartily concur.

DR. LOUIS HUBERT: I have listened with much interest to Dr. Hurd's paper. My work in diathermy has not been confined to the tonsils, but mostly to the procedures which Dr. Hurd refers to in his paper as being superior to surgery. I agree with him and believe that anyone using these methods will be as enthusiastic as I am.

Dr. Hurd spoke about cysts. We have had a large cyst of the pharynx. I used diathermia similar to the method described by Dr. Hurd and after one treatment we were astonished at the result. I can also corroborate what Dr. Hurd said about adhesions within the nasal cavity. We have had a patient with extensive adhesions within the nose, for which the electric cautery had been used without success. However, after the use of diathermy the adhesions never returned. Diathermia is also useful in reducing granulations after operation on the sinuses and in keeping the sphenoid open. I have also used this method for the removal of polyps, especially in cases of polypoid sinusitis. We all know that in these cases polyps recur even after what appears to be a thorough removal. Instead of telling the patient that some more polyps have to be removed, it is better to destroy them by diathermia. The same thing is true in tonsillectomy. If after the surgical removal of the tonsils a piece of tonsillar tissue is left, and you do not want to tell the patient that you have done so and have to remove it, a simple and single application of diathermia will remove it.

I also used diathermia in a very rare and unusual condition, namely in a patient with a lingual thyroid. We know that its surgical removal is followed by myxoedema. I used the coagulating current very carefully from time to time until the mass shrank and the discomfort within the throat was relieved. No myxoedema followed.

I have also used diathermia for the intranasal opening of the maxillary antrum. In doing this great care is necessary. I have somewhat modified the method that I have recently described. The roentgenologist tells me whether the nasoantral wall is thick or thin. If thin, there is no danger in using the electrified trocar. If the nasoantral wall is very thick, it is safer to do a regular intranasal antrum operation and apply the electrified trocar to the opening thus made, in order to prevent this opening from closing.

In reference to the use of diathermia on tonsils I agree with Dr. Hurd. He advises this method only in certain cases. If a patient, who is a good surgical risk, comes to me for the removal of tonsils and says: "I want you to dry up my tonsils by electricity," I explain to him or her the process of coagulation and then ask the following question: "Do you want to remove your tonsils by approved surgical means or by sloughing?" Patients usually decide for surgical measures. If, however, they insist on diathermy, it is up to the laryngologists to do it. If laryngologists will not take up this work, it will be done by others who are not competent to do it.

DR. HENRY M. SCHEER: There is no question about the fact that electro-surgery is now a definitely accepted procedure, and that when handled by men who know how and when to use it, good results can be obtained in certain selected cases when used for definite selected purposes. We know that in the hands of men like Dr. Hurd, one can get good results. I am sure he will tell you too that in many of the cases he did not get the desired results.

The crux of the situation, however, lies in the fact that we ought not to undertake to use it because the patients want it, but only in those cases that deserve to have it used. In this respect I feel that the cases that require it in the nose and throat field are few as compared with those that deserve the good orthodox surgical procedure. The reason for so many of the bad results obtained lies in the fact that the greater number of these cases have been done and are being done by men in the two groups mentioned in Dr. Jone's paper tonight: the third and fourth; the third. The otolaryngologist who is the last to learn the procedure, and the fourth, the general practitioner who learns the procedure to make a livelihood and to hold on to his patient.

We are here in the Academy of Medicine to learn whether it is a worthwhile procedure, or one that will fall by the wayside after having been given fair trial. I would like to report a case of a man forty years of age, who had never been sick. A perfectly healthy individual, who in August last, went to see a doctor for axillary furunculosis, for which he was treated by this doctor with vaccine therapy. The doctor found some hemorrhoids and injected them and they disappeared. He then looked about and found a pair of large tonsils, and although the man had never had a sore throat in his life to his recollection, nor any other complaint, he gave an electrical treatment to one tonsil one week and the next week one to the opposite side, and the third week treated both tonsils. During the first two weeks of treatment, the man felt well, but after the third treatment he had a severe sore throat and in the following twenty-four hours it became agonizing. He went back to the doctor, who advised gargling and local treatment. A few days later the patient complained of agonizing pain in the head and throat. He went back to the doctor and the same advice was given.

Then the patient came to me. I admitted him to the Polyclinic Hospital on October 17th with marked swelling on both sides of the neck and difficulty in opening the mouth.

Case Report: H. P., white, male, age 40 years. Was admitted to the hospital on Oct. 17, 1932, with history of having had three electro-coagulation treatment of tonsils at weekly intervals. Last treatment was ten days before admission. C. C.: Sore throat and enlarged and tender cervical glands. Right—three plus. Left—two plus. Ten days duration. P. H.: No previous history of operations. No previous illnesses. F. H.: Negative. Ears, Eyes, Nose—Negative. Pharynx: Both tonsils inflamed, and covered with sloughing mass, redness extending to pillars. The soft palate and uvula was edematous. Free pus from each tonsil. Neck: Anterior cervical glands on both sides enlarged and tender. Larger on right. Chest: Negative. Heart: Negative. Abdomen, etc.: Negative.

Provisional Diagnosis: Acute tonsillitis. Acute cervical adenitis.

The temperature on admission was 99 degrees. The following day, the temperature rose to 102 and 103 degrees. The throat reaction and swelling of neck with resulting dysphagia increased. On the 4th day, the swelling on the right side of neck was incised. No free pus was obtained. Drain was inserted and hot wet dressings were instituted. Following this the patient had chill and temperature rose to 106 degrees. White count, 23,600; Polys., 82 per cent; Blood culture: Negative.

The temperature remained high for the succeeding days, ranging from 102 to 105 degrees. There was moderate amount of drainage from the wound. Swelling extended from right side of face to clavicle below and protruding to midline, front and back. Patient was extremely ill. Blood culture on Nov. 11, 1932, was negative. R. B. C., 3,500,000; W. B. C., 26,800; Polys., 78; Lymps, 22. Culture from wound was staphylococcus aureus.

Diagnosis: Deep cellulitis of right side of neck. Mercurochrome injected in external wound came through tonsillar and pharyngeal region.

On Nov. 11, 1932, multiple incisions were made into swelling. One long incision along anterior belly of sternomastoid muscle and smaller incisions anteriorly, and in posterior triangle. Another incision low in the anterior triangle a little above the clavicle to drain a deep pocket here. Drains were inserted and hot wet dressings continued. A blood transfusion was given at this time. Patient continued very ill. Considerable tissue sloughed out of area involved, along with profuse discharge of pus, and wounds soon began to look better.

On Nov. 15, 1932, patient developed erysipelas about wound, which spread over face and scalp, lasting about one week. He was given daily injections of erysipelas streptococcus antitoxin for first three days of this complication.

Following this, the patient developed a series of furuncles and boils all over the body, which lasted until present date.

Patient was discharged Dec. 8, 1932. Temperature had been normal for past two weeks. Cellulitis of neck about well. Throat reaction had entirely subsided. The tonsils and pillars are a mass of scar tissue. The major portion of both tonsils still remain and are imbedded in this mass.

Dr. Hurd asked me to bring this case up to point out the very severe results that may occur in some of these cases. One must be very careful in selecting cases, and apply the electrical therapy only in those that actually deserve it.

(Dr. Scheer then told of a man of 68, who had been wanting for two years to have an electro-surgical procedure on his tonsils. There was no reason why it should be used, for he was a healthy man with a good blood picture. His tonsils required removal. The matter was explained to him, and he finally consented to have them removed surgically.)

DR. JACOB BRAUN: For a long time the rhinologist has ignored endothermy or, as it is more frequently called, diathermy. Untrained enthusiasts hitherto had preempted this field. By reason of their unfamiliarity with the anatomy and functions of the structures they essayed to treat, they often caused irreparable injury. Because of the exaggerated and unscientific claims made for endothermy, competent observers eschewed investigation for a long period, of this valuable therapeutic agency. The paper presented tonight is therefore highly significant.

More general application of endothermy in the domain of rhinology has been rewarded by gratifying results. In the nose, removal of the posterior tip of the inferior turbinate, submucous reduction of hypertrophied turbinates with preservation of the functionating epithelium, troublesome synechiae, varicosities in the nasal and septal mucosa, have yielded to its use. In the pharynx and larynx, lymphatic hypertrophies on the base of tongue and the pharyngeal wall, benign growths in the larynx and many other conditions where limited, safe and effective destruction of tissue is required, have been destroyed with little or no reaction.

The tonsil, however, has been the chief object of its therapeutic attack. This so-called new technic has been so well exploited to the public that patients now frequently dictate the method by which they are to be treated.

It is to this phase of the subject that I will more particularly direct my remarks.

The general application of endothermy to all tonsillar hypertrophies or infections is to be condemned. It will not supplant surgery. When contra-indications to surgery make it a satisfactory solution of an occasionally doubtful risk, it should be employed.

The several methods of removal of the tonsil by endothermy are:

a. The mass removal wiht the mono-polar current—electro-desiccation. This method has absolutely no advantage over competent surgery. The shock and danger of secondary hemorrhage are greater, and the convalescence protracted and uncomfortable. Because of the possibility of damage to adjacent tissues very considerable skill is required.

b. Electro-coagulation. This method has the advantage that it is comparatively safe and that it does not interfere with the patient's regular occupation. Contrary to the general opinion, its technical demands are as exacting as those of a well performed surgical or electro-surgical tonsillectomy. Treatment being long drawn out, it may be abandoned before a satisfactory end result is obtained.

Its application, even in skilled hands, is neither so easy nor so completely safe as its early proponents have urged. No one should attempt it unless prepared for every possible eventuality of tonsillar surgery. Hemorrhage can be very severe, and sometimes is difficult to control. It may occur several days to two weeks after treatment.

c. Electro-surgical tonsillectomy. The removal of the en masse without destruction to the tonsil and without injury to the tonsillar bed.

The method and instruments must be simple, the current application short.

I have been using for about four years a modification of the snaretome technic.

The changes are the replacement of the steel wire with No. 35 nichrome wire, and the insulation of the distal end of the snare cannula with rubber tubing. Rubber gloves are worn.

This technic leaves a smooth, glistening tonsillar fossa, and except for a white line around the limit of the tonsillar attachment, the appearance is that found in a cold wire snaretome operation.

This method is not applicable to tonsils that are deeply imbedded and bound down by adhesions. The thickened and fibrosed capsule requires prolonged

application of the current, with cooking of tissue with resultant necrosis. This method is quick, safe, bloodless in most instances. The convalescence is short and uneventful.

DR. JULIUS I. KLEPPER: There is no doubt that both Dr. Hurd and Dr. Morrison have a wide experience in diathermy. We cannot positively state indications and counter-indications in all instances, nor can we guarantee that results may not have been better with true surgery without diathermy; among those borderline indications, we may say that advanced age is not a true indication for diathermy alone.

A case of a woman patient about 65 years of age treated for rheumatism was referred for removal of tonsils. One application of diathermy was made by Dr. M. The patient suffered tremendous pain for a week. The neck became very swollen, and she absolutely refused to return to have another treatment. She came to us to remove the tonsils in the regular surgicay way, and this was done. For her age, she behaved about as normal as could be expected.

DR. ARTHUR J. HERZIG: Dr. Hurd is to be congratulated on the way in which he presented the subject of Surgical Diathermy in Rhinopharyngeal conditions and results obtained—good, bad and indifferent. I shall limit my discussion of surgical diathermy to that of the tonsil. If one believes in removing the capsule of the tonsil, then I think a surgical tonsillectomy is indicated; on the other hand, if you desire to retain the capsule, then the electric method is indicated. Aside from malignancy or angiomata, I don't see the advantage of diathermy over the old cautery with a well insulated tip.

DR. J. M. LORE: I would like to know Dr. Hurd's opinion of the effect of the current on bone. I ask, because Dr. Hubert has advocated its use in the sphenoid region in post-operative cases and also in the case of polypoid adenitis. It seems to me that in view of the fact that the current is apt to cause an osteomyelitis or necrosis of bone, that the use of this current in this region is attended with some danger. Personally, I feel that I would rather not use the current in this region because of the serious potentialities.

DR. L. M. HURD: I was speaking of some fourteen conditions in which diathermy can be used. Some of them are an advance over older methods. Tonsil coagulation was just one of them. We should not criticize the tonsil results one sees too harshly for two reasons. First, you only see the poor results, and second, so many men are doing it who have no business attempting such work because they have had little experience with diathermy and no training as laryngologists. The method has a limited place and the laryngologist should know how to do it properly. When some institution reports 30,000 cases with their complications like the Manhattan Eye and Ear has in a similar number of surgical tonsillectomies, then the question of the comparative merits of the two methods will be settled.

Dr. Hubert spoke of his method. We are trying the method for antrum punctures as we would try any method that seems to have merit.

Replying to Dr. Lore, we should be very careful when near cartilage and bone because both are easily devitalized by diathermic heat. When a patient comes to me and requests that his tonsils be removed by diathermy, if he is in good physical condition, I ask him why take at least four months with the repeated sore throat, when with surgery it is all over at once and the throat is sore for about a week.

Dr. Morrison's patient with cellulitis quickly subsided, Dr. Scheer's patient nearly lost his life. One hears rumors of complications from diathermy that are never reported.

Replying to Dr. Braun, with the snare we use there is so much insulation that it is clumsy. If I had another model made I would only have the cannula insulated.

DR. ROBERT H. FOWLER: The truth is what we are seeking; it is very evident that Dr. Hurd, in preparing his paper, set out to give us as much *truth* as possible about the use of electricity on the structures of the nose and throat. He has established through well considered effort the value of electricity for removal of postoperative synechia and for many other purposes, such as the shrinking of hypertrophied turbinates. He still keeps an open mind on the point which I would like to discuss, namely, as to whether electrocoagulation is a good substitute for tonsil surgery.

The fair-mindedness of the speakers this evening is noticeable, the absence of animus even on this moot question is an example which I shall try to emulate; please take my remarks in that spirit.

One of the proponents of electrothermy answered the question I propounded to him here: "If you had ten patients with chronic infected tonsils and destroyed the tonsils with a series of electric treatments, how many would get a result satisfactory both to the surgeon and to the patient?" He said: "Perhaps seven." Now that seems to me eminently fair, especially as he followed it by saying: "One is apt to exaggerate the good results of anything which is his hobby." The transparent honesty of his reply gives me a feeling that we are getting nearer together in our search for truth, those who use electricity and those who use the orthodox surgical methods.

Some of us who do not use electrothermy have very definite and well grounded opinions as to its value. We do not see the seven out of the ten—the seven who are satisfied—it is the other three that come to our attention with embarrassing frequency.

Truth turns up in unexpected places. Let me illustrate by telling a story of what happened to the gunners that put out our decoys at Fire Island last week. They were very disappointed because the day before they had lost a goose, though they had winged it. It wasn't only the loss of the goose that grieved them, but the crippled goose had, as they said, "flopped over the dunes," and a boy walking on the beach had killed it, though he had no decoys and by rights should never have had a look at it. The question arose as to who owned the goose, and with excellent sportsmanship, "finders are keepers," they decided that the goose belonged to the boy and they gave him due credit.

Now, gentlemen, I want to show you a goose that someone else winged; you see it in this little slide (holding it up), a "bird in hand," and I am playing the part of the boy who had no decoys. *This is the corpus delicti*, a cogent bit of evidence for those who are seeking the truth.

These are the facts: (1) a patient suffering from rheumatism was told last year that the tonsils would be taken out by surgery or electricity—the two methods were equally good; (2) ten high frequency treatments were given, the rheumatism continued and the patient was not satisfied; (3) examination showed small buried infected tonsils with fluid in the crypts that appeared to be pus; (4) the patient was given a choice to continue with the electric treatments or to have the tonsils removed surgically, this time with an increased likelihood of hemorrhage, and chose to take this risk; (5) the tonsils were removed by dissection and snare, and severe hemorrhage followed within twenty-four hours. These five points cover the history, and a word will cover the important findings in the microscopic sections.

Here on this side is a pair of tonsils cross-sectioned two months after a series of electric treatments. In order to make clear to your eye at a distance the findings of the two slides, here is a larger diagram that I have made, on the upper half of the sheet, a triple section of tonsil (which you will find on one slide) from an *average case*, after removal. Even at a distance you can see that the upper lobe is clean, there is a remnant of muscle at the hour glass constriction at the junction of the upper and lower lobe where it inserts. This is a normal anatomical insertion, and a wisp of muscle is shown over the lower lobe. The so-called capsule itself is, in this case, a thin layer of pharyngeal fascia, and continuous with it are shown the light trabeculae, the fibrous structures within the substance of the tonsil. This upper half of the chart servees for orientation, these are the findings in an *average* careful dissection, the muscle is stripped off the upper lobe but remnants are left where the muscle *inserts;* that is, where it has its normal anatomical attachment.

Now, in contrast, look at the lower half of the chart, where you see the cross sections of the *unusual* tonsils that we are discussing, which were removed after several electric treatments had been given. Muscle is found attached to the whole submerged surface, upper and lower lobes, though the same effort was made to get a muscle free dissection in this case as in the other. Let me stop here to call your attention to this fact, that the attach-

ment of muscle over the upper lobe (after electrothermy) is clearly pathological. The capsule itself is greatly thickened, as are the trabeculae or fibrous tissues within the tonsil. It is significant that a ring of scar tissue has been formed at one place. Under the microscope it is seen that the vessels are thrombosed, they are increased in number, there is odema, exudate of leucoccytes, and there are still infected lymphoid follicles. In other words, both specimens, with and without electric treatments, show inflammatory infiltration.

If these two things are clear, if you see that the submerged surface of the tonsil is thickened and attached to surrounding muscles, and that the portion of tonsil that has not been turned to scar is still infected, it is sufficient. These points will serve.

I leave it to you to decide their importance.

My case rests.

As the speaker stepped down from the desk a voice was raised in question: "What was the *standing* of the practitioner who gave the electric treatments?"

Dr. Fowler: "The answer is, a surgeon of the *highest* standing. I think you mean to imply that the electric work might have been done by a general medical man or a chiropractor. No! it was fortunate that in this case my embarrassment was lessened by my being able to recommend the patient to go back to the same doctor, either for further treatment or for operation. I would not have felt it right to do that if I had not believed my colleague's standing to be of the highest, and now I, here, vouch to you for the unquestioned ability of this surgeon as such."

"It was not a case that I was anxious to operate on, the patient is a relative of a friend of mine who was greatly concerned about the question as to who should do the operation, and I was overruled in suggesting that the first doctor was the proper person. The patient had also lost confidence after ten electric treatments and said: "I do not want to be *experimented* on any more, rather the operation with the attendant risk of bleeding."

My experience, in private practice, consists of having had half a dozen such cases after therapy, including one X-ray, one radium, and four electrothermy, all of them had hemorrhage following operation and all recovered, and the character of the bleeding, as you would expect after studying the pathological slides depicted in this chart, was severe.

Electrothermy is not designed to make it easy for surgery that is to follow.

Dr. Jacob Braun: I would like to know whether the patient had been discharged as a completed case by the laryngologist.

Answer: No, the patient had not been discharged as a completed case, and at first I encouraged him to continue the series of treatments, but he had lost confidence. I don't think that you can say, from the evidence that we have, that another ten treatments might not have been satisfactory, but at all events, the tonsils are out and that gives us the chance to study the result of electrothermy at this incomplete stage.

I started my discussion of Dr. Hurd's paper by stating how fair minded I thought the protagonists of electrothermy were getting to be, and I promised to do as well myself. We are all in the same boat. I have long dreamed of taking out tonsils by electricity, laugh at me if you will, but let me tell you that *my* dream differed in one particular from anything that has been described or practically used, for in it the capsule was *insulated;* a fluid was injected just as we inject the solution for a local anesthetic today, flooding the capsule. This, in the dream, was transmuted into asbestos and conveniently and completely formed a fire curtain to protect the nearby anatomical structures, arteries, veins and muscles, so that the electric current could be applied without fear of deeper penetration.

Now I am quite free to say that when this becomes practical I expect to use electrothermy in certain cases, for only today a patient was in the office who said: "When you learn this modern electric means of removing tonsils I want you to take mine out," and I said: "Madam, we have not perfected the use of electrothermy for this particular purpose as a substitute for good tonsil surgery, *as yet*, but come in again next month. I am going to a meeting at the Academy tonight to hear the last word on this subject, so come back again, please, next month."

THE NEW YORK ACADEMY OF MEDICINE.

SECTION OF OTO-LARYNGOLOGY.

Meeting of January 18, 1933.

The Symptomatology and Diagnosis of Acute Mastoiditis. Dr. Richard T. Atkins.

(To be published in a subsequent issue of THE LARYNGOSCOPE.*)*

Diagnostic Aids in Acute Mastoiditis: X-ray. Dr. Frederick M. Law.

(To be published in a subsequent issue of THE LARYNGOSCOPE.*)*

Diagnostic Aids in Acute Mastoiditis: Laboratory. Dr. Andrew A. Eggston.

(To be published in a subsequent issue of THE LARYNGOSCOPE.*)*

Differential Diagnosis in Acute Mastoid Disease. Dr. Marvin F. Jones.

(To be published in a subsequent issue of THE LARYNGOSCOPE.*)*

DISCUSSION.

DR. JOHN B. RAE: It would seem that the subject has been so completely covered that anything I have to say would be rather in the nature of bringing coals to Newcastle.

It is evident that when all the classical symptoms are present in a given case there will be no difficulty in arriving at a correct diagnosis. Difficulty in diagnosis will arise only when a majority of these classical symptoms are absent or when their interpretation is obscured by complicating conditions.

It is essential that the examiner should have a well ordered method of investigation. This will begin with a definite history of the onset of the ear condition; the amount and character of pain, if present; whether pain interfered or still interferes with sleep; the date of spontaneous rupture or of myringotomy; the amount and character of the discharge; the course of the temperature, and the pulse rate. The condition of the tongue is important.

Examination of the canal will show the amount of pus accumulated since the last cleansing. On its removal the drum membrane is inspected. The landmarks may or may not be recognized. Location and extent of a perforation are noted, and one determines whether or not the drum membrane is bulging, and also whether or not the postero-superior canal wall is prolapsed. One estimates the amount of discharge by the rapidity with which the canal refills after wiping or after inflation by the Volsalva method.

Examination behind the ear may or may not show edema or fluctuating subperiosteal abscess. One seeks for evidence of tenderness on pressure. This is usually an early and fairly constant symptom. It is probably due to direct compression of the inflamed bone tissue and not to periostitis, which is a late symptom. It should be sought for over the whole surface of the mastoid, with special attention to the regions of the antrum and the tip where it is most frequently marked. In applying pressure, one must make it inwards and backwards, so as to avoid disturbing the cartilage.

In the majority of cases diagnosis can be made on the clinical findings alone; indeed, one is frequently obliged to place entire dependence on these. But in doubtful cases proper use should be made of the additional information to be gained from the x-ray and pathological laboratory findings. As is well known, there occurs a loss of hearing in these mastoid cases out of proportion

to the apparent middle ear involvement. Also, the findings on the affected side should always be compared with those on the other.

This systematic examination having been made, one is justified in saying that diagnosis is made on the sum of the symptoms and that operative interference is determined by their persistence. This does not mean that all symptoms persist. It is notorious that urgent symptoms often subside after spontaneous rupture of the drum membrane or after myringotomy, and that operation must be urged after what is regarded by the bystanders as distinct improvement. In addition, the patient acquires a certain degree of tolerance, and may eat and sleep well, and go about his daily duties for weeks while the subject of a progressive destructive process in the mastoid. Further, one has sometimes to deal—and this especially applies to clinic cases sent into the wards for observation—with a purposeful effort of the patient to deceive the otologist. It is part of the defense mechanism of the patient who has had the opportunity to observe other patients sent to and returned from the operating room. In making tests for tenderness on pressure, the spoken answers are not always reliable and one should note the facial expression and the shrugging movement of the shoulder when pressure is made.

How are we to determine operation in those cases in which urgent evidence is lacking?

It seems that, granted an ear, we must ignore the negative and place due stress on the few positive findings. In this way the persistence of any one symptom may be the real operative indication. In little children, the persistence of temperatures may be the indication; while in the adult the character and amount of the discharge—showing that it comes from a space more extensive than the middle ear—or persistent tenderness may be the deciding factor. Other examples will occur to you.

Total absence of tenderness on pressure must be accounted for. If we concede that tenderness is due to direct compression of the inflamed cellular structure, its absence may be explained by the physical make-up of the mastoid itself. We expect little tenderness in an undeveloped or sclerotic mastoid. An extremely thick cortex offers another reasonable explanation, as also does a forward and superficial sinus, leaving little space for cells. X-rays should prove a valuable help in these cases.

With regard to differential diagnosis, I wish to emphasize two common sources of confusion. With a middle ear and suspected mastoid, the occurrence of a furuncle on the posterior wall with post-auricular edema, will add to the difficulty. In the absence of urgent symptoms, these patients should be hospitalized, the furuncle incised, wet dressings applied, and observation continued over a period long enough to make the differential diagnosis clear.

Again, post-auricular abscess in little children is not always due to mastoiditis. If resulting from a cortical perforation of the mastoid, the appearance is generally characteristic. The periosteum being bound down at the squamo-mastoid suture, the auricle is tipped upwards and forwards. If in doubt, the abscess should be opened through a regular mastoid incision, and if the periosteum is found to be already elevated the mastoid operation should be done.

DR. CLARENCE H. SMITH: Mr. Chairman, Ladies and Gentlemen, the subject has been so thoroughly covered that there is very little to add except to emphasize a few points which have been mentioned.

I have found the following simple measure of service in helping to diagnose involvement of the mastoid: rub the tip of the index finger lightly over the mastoid process and see if the bone is sharply defined to palpation as in the normal, or, as is often felt in the diseased mastoid, if there is a sofetened velvety feeling obscuring the outline of the bone, indicative of a thickened periosteum.

I experience difficulty in explaining away the fetish of the necessity of fever being present in mastoiditis, from the minds of parents and often of family physicians.

It has helped me in diagnosing external otitis where the canal is so swollen as to prevent inspection of the drum, to test the hearing for voice and whisper. If the patient hears well we can feel fairly safe that there is not much likelihood of the post-auricular swelling being due to mastoiditis. Of course, this measure is not applicable in children, but furunculosis is comparatively rare in childhood.

In external otitis with purulent otitis media, accompanied by post-auricular swelling, I think the furunculosis is much more likely to be the cause of the tumefaction, especially in the adult. I like to give the patient the benefit of the doubt, treat the furunculosis energetically, and wait developments.

I recall the case of a boy of three, a couple of years ago, with a profuse, greenish discharge from his left ear, markedly swollen canal walls, through the anterior wall the pus could be seen draining. Examination of his throat showed a large peritonsillar abscess, which was the source of the pus.

The diagnosis of operative mastoiditis in an atypical case is often quite difficult. It is here that the services of a good roentgenologist are so valuable, and it is unfortunate that reliable X-ray work is not more universal.

I think the dictum of Skillern as to the otologist interpreting roentgenograms ideal, if feasible. My own limited ability in this, as well as the very poor material submitted at times, makes me quite willing to accept, however, as the best evidence, the reading of the plates by the man who made them.

If referred ear pain occurs when there is otorrhea we may have a real problem. A complicating empyema of the antrum or of the sphenoidal sinus can cause pain in the ear. A lesion situated in the area of the trigeminal, of the glosso-pharyngeal, or the superior laryngeal branch of the vagus may produce pain referred to the ear. An unerupted wisdom tooth is often responsible for earache.

Occasionally one sees a patient complaining of earache on whom the diagnosis of hysteria has to be placed. Recently I was consulted by a middle aged woman who had had in the last four years all her nasal sinuses except the frontals operated, her tonsils removed, most of her teeth, and her nasal septum. She complained bitterly of long standing pain in and behind her left ear, which had some time since been the seat of a purulent otitis of eight weeks duration. She apparently evinced mastoid tenderness. On examination her drum was free from inflammation and her hearing was almost normal. Her sinuses had been very radically operated. I could find no cause for her pain and told her so. X-ray examination by Dr. Law was equally non-informative. She went away, really I think, rather disappointed because she was not going to have her mastoid operated.

Dr. Isidore Friesner: The section is to be congratulated on the selection of the men who have carried on this symposium, for the presentation has not only been complete but brief. A symposium like this, entailing a discussion of diagnosis, differential diagnosis, roentgenology and the laboratory, frequently degenerates to a state that reminds me of the Darkey who hailed his wife to court for a divorce. The Judge asked: "What is the trouble?" He replied: "You know, Massa, she talks all the time. When I gets up she talks; and when I come home she talks; and at night she talks." Then the Judge asked: "What does she talk about?" and he replied: "Judge, she don't never tell."

I am sure Dr. Eggston did not purposely omit the hemoglobin as an indication of the severity of the infection.

Answering Dr. Jones' challenge: I would say that six years ago I had the honor of presenting the first study of the chemistry of pus that was ever made, with the idea of determining the differences between pus coming from a suppurating bone focus and pus from soft part abscesses. I am happy to say that that presentation has been substantiated a number of times, most recently from the University of Sendai, which has one of the best equipped chemical laboratories in the world. I hope that some time we will have a test so simple and so easy of accomplishment that one can readily tell what the calcium content of pus from the ear is, without going through the long complicated laboratory methods necessary at present to make such a determination.

DR. WESLEY C. BOWERS: All the points in the symptomotology of mastoiditis have been thoroughly covered and there is little to add. I would like to emphasize a few important points. It has been stated that the diagnosis of involvement of the mastoid is obvious. This is true. It is a simple matter to determine when there is involvement of the mastoid, but to determine when this involvement is such as to demand surgical intervention is a problem not so obvious.

As we all know, there is not one of the general and local symptoms (with the exception perhaps of a subperiosteal abscess and marked narrowing of the fundus) which do not frequently disappear spontaneously. This being the case, it is evident that the diagnosis of a surgical mastoid does not depend on one or more of the general and local symptoms, but upon the degree of severity of the symptoms, the persistency of the symptoms or the recurrence of the symptoms. Added to this we have to consider the type of infection, positive X-ray findings and unusual laboratory findings.

For example, take the typical case, pain in the ear, high temperature, rupture or myringotomy, marked mastoid tenderness, profuse discharge. This is mastoiditis but not necessarily a surgical mastoid, as we know that most of these cases recover spontaneously. If the tenderness persists or recurs, the discharge persists or recurs, the fundus shows change, then we have a surgical mastoid. though even some of these recover spontaneously. During the first week of an involvement of the type mentioned above, in the presence of high temperature, marked prostration, exquisite mastoid tenderness, exceedingly profuse discharge, we are between the devil and the deep sea. We know that there is danger of the condition spreading to the meninges if we do not operate, but in my opinion the danger of extension to the meninges is greater if the operation is performed at the period before nature has had a chance to wall off the infection to some extent.

On the other hand, the Pneumococcus group III infection in the mastoid requires prompt decisive action in spite of perhhaps mild symptoms, both local and general. Though I have seen a number of Pneumococcus group III infections in the mastoid recover spontaneously, I feel that the sooner the mastoid is operated on in the presence of this infection the better, otherwise we will be taking chances with the life of the individual for at least three months. Following this infection I have seen abscesses in the petrous bone and in the mastoid as late as three months after the primary infection with practically no symptoms in the interval.

Next we have the type in which most of the general symptoms and all the local symptoms, with the exception of the discharge have disappeared. Here again we find the persistence of the discharge with very little if any variation, changes in the fundus and the recurrence, perhaps, of one of the local or general symptoms which will enable us to determine whether this is a surgical mastoid. Lastly we have the type in which there are little or no general or local symptoms, very slight if any changes in the drum, no discharge and so on, yet one or more symptoms persist or recur; from day to day the appearance of the drum membrane changes, one time practically normal, another time slightly red and full in Shrapnells; pain over that side of the head never severe but peristent and recurring, not relieved by inflation.

It is the persistency and recurrence of symptoms, general or local, together with perhaps changes in the fundus which frequently help us to decide whether there is present a surgical mastoiditis.

DR. S. J. KOPETZKY: It would be unusual in a group as large as this if there did not develop varying viewpoints. In no sense taking particular exception to the excellent presentations made here this evening, which covered so wide a field, it would seem necessary, in order to complete the record, to present a slightly different point of view.

I cannot quite conceive of the pathological lesion of an otitis being limited to the anatomical structures of the tympanic cavity and then subsequently involving the anatomical structures of the mastoid process. I find substantiation for my opinion in the older work of Scheibe and, since the advent of the

roentgenogram, in the reports of many observers who noted involvement of most of the mastoid cells simultaneously with the development of the otitis.

I look upon all infections of the middle ear spaces as a pathologic entity, complete in itself, and the involvement embraces the tympanic cavity, the aditus and the mastoid cells to a greater or lesser degree. Such an infection either resolves or it presents evidence requiring surgical intervention.

It was brought out tonight very distinctly that the anatomical structure underlying the pathology is an important factor in governing the type of lesion which the infection will produce and the clinical course it will pursue. That hint was clearly given by Dr. Law and deserves attention. To re-state it concisely, the course of an otitic infection, and the nature and type of lesion it will present, is dependent upon the anatomical structure of the given mastoid process, modified to a degree by constitutional factors and the kind and nature of the invading microrganism.

A pneumatized bone may break down and present a coalescence. A pneumatized bone may show an attic perforation and give an acute necrotic otitis; and, in this case, even if surgery becomes necessary and a simple mastoidectomy is performed, a dry middle ear will not take place and should not be expected. On the other hand, the non-cellular process cannot coalesce and a classical coalescent mastoiditis is impossible in ebonized bone; nor will superficial periostitis develop to give signs of "furring" to the touch and pain on pressure. Hence, in reaching a diagnosis, the first logical step would seem to be an effort to determine the type of anatomical structure the patient presents, because definite sequelae follow distinct types of anatomical structure.

Some one indicated a valuable diagnostic sign when he spoke of the reappearance of the ear discharge immediately after its removal by cleansing. Let me add to that observation another sign which I have found very valuable. If, with the ear fundus under observation, and after careful cleansing of the canal of its secretions, pressure is put on the internal jugular vein of the same side, where there has been a breakdown of cells and there is pus retention there will ensue a jetting spurt of pus from the opening in the drum-head. I have found this sign invaluable in the diagnosis of pus retention and cellular breakdown and, taken together with other symptoms, have used it as a determining factor in diagnosis and indication for operation.

Since I am in complete agreement with Dr. Rae that in the majority of cases a clinical diagnosis is possible from the bedside study of the patient, I use the roentgenogram to determine the anatomical structure which is presented. Because of the knowledge recently acquired of the lesions in the petrosal pyramid and the necessity of knowing the state of these structures at the commencement of the disease, one plate is taken, which is designated the "key plate," to give all this information. This is a base plate. On it can be seen both mastoid processes, their anatomical type, and both petrosal pyramids, whose structure is also thus registered for subseqent comparison, should their involvement become questioned.

In the hands of Dr. Law and other experts like him who have training in otology, the significance of haziness in acute otitis will not be misleading. Generally, however, it is accorded a significance not warranted by our knowledge of the pathology.

Dr. Law made, in passing, a very pertinent observation in the case he cited in which there had been recorded a breakdown of cells and then, after an interval of some years, another plate was taken which showed a regeneration of cellular structure. If that observation is correct, we must revise our entire theory of pneumatization of the mastoid process. Resolution after cellular destruction in the temporal bone has been believed to take place by fibrous tissue replacement in which ossification might to some extent occur; but the reformation of cells with defined cell walls has not heretofore been observed and needs explanation.

Skillern's dictum that all of us should read roentgen plates is difficult to accept when we note how few roentgenologists are willing to read another radiologist's plates. He usually wants to take his own plates and read them. However, we can become habituated to reading one man's plates. We will

get to know and evaluate his means of expressing shadows and have a standard, each of us for himself.

It is a pleasure to hear Dr. Eggston and his opinion on the use of subcultures. I agree that in a given case not much knowledge is obtained by a subculture; but, if they are done regularly the trend which the infections run is determined and that information, in addition to the study of the case at the bedside, gives one diagnostic and prognostic data. I like the von Schilling count. When this is used in conjunction with the sedimentation test, you have at your hand a very fine indicator as to the condition of your patient. Neither is specific, but between the time of operation and the clinical onset of complications, when clinical signs may be transient, these two tests give warning and set you on guard.

The blood culture is an old story but with a new angle, since we are paying attention to the anatomical structure involved in our lesion. We find positive cultures in the mastoid, most often where we have the diploic type of bone. After mastoidectomy the blood is negative. Clinically, these cases usually present a septic type of picture too. Of the invading organisms, the hemolytic streptococci are the usual invaders of severe infections; although where a hemolytic staphylococcus is encountered, a marked sepsis will be encountered.

While treatment is not included in our symposium, blood transfusion has been mentioned. May I add that, when used, they should be small, repeated transfusions rather than large ones.

Finally, in the influenzal otitis, a differentiation should be made between the bulging drum and blebs on the drum. Where possible these blebs should not be incised.

DR. GEORGE WOLF: In discussing differential diagnosis no mention has been made of herpes zoster auriculae, Hunt's disease, also spoken of as herpes oticus. This condition can be, and at times is, mistaken for acute mastoiditis. I knew of one such instance where the patient's mastoid was operated on.

DR. SAMUEL ROSEN: Positive blood cultures taken during the first forty-eight hours following mastoidectomy would be of questionable value. Libman in 1912 took blood cultures in uncomplicated mastoiditis during the first 24 hours after operation and found many positive. It would be dangerous to place too much importance upon this. Blood cultures taken too soon after operating upon any suppurative focus may be positive. This has been found after tonsillectomy. One should wait at least 72 hours after mastoidectomy to have any real significance paid to positive blood culture.

Dr. Rae said something which interested me—"That one has to make up one's mind as conservatively as possible whether there is pus in the mastoid and act accordingly." The absence of pus in a mastoid, however hemorrhagic it may be, should be noted as an error in diagnosis rather than be termed hemorrhagic mastoiditis. The finding of pus during the mastoid operation justifies the operation. The absence of pus in the mastoid does not constitute surgical mastoiditis.

DR. RAMSAY SPILLMAN: The last speaker made the statement that radiologists will not read each other's films. I challenge that. I will read anybody's films provided they are good. But I am frequently asked by colleagues to read films made by some doctor who does x-ray work only casually, made on dirty and battered intensifying screens, films which one has difficulty in telling what part of the body they show, and often made at a fee that I as a specialist would not think of asking. There is nothing in it for the roentgenologist in such a case except to let himself in for a share of the responsibility if the diagnosis is in error. I disagree with the statement that roentgenologists will not read each other's films. When a reputable roentgenologist refuses to read a film made elsewhere, the only reason is that the film is not fit to read.

(To be continued in May issue.)

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EXPERIMENTAL STUDIES IN HEARING.

I.—The Threshold of the Reflexes of the Muscles of the Middle Ear.

II.—The Hearing-Loss After Extirpation of the Tympanic Membrane.

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St. Louis.

In a preliminary communication[1] a series of experiments on hearing in mammals was announced; the reflexes of muscles of the middle ear to stimulations by tones were to be used for testing the hearing ability after determined operations on the hearing mechanism.

Systematic studies in this line seem not to have formerly been carried out; it is true that a good deal of work on the reflex contractions of the tensor tympani and stapedius muscles has been done, but apparently only with the purpose of ascertaining the function of the muscles. This goal has not yet been reached, because the different theories that have been proposed evidently are insufficient for explaining the known facts, but we provisionally leave this consideration out of our field, at least until sufficient facts have been established, which together with the already known ones, may give a sound basis for theoretical arguments. In this first series of papers we shall use the reflexes of the muscles of the middle ear simply for testing the hearing ability of the experimental animals.

The possibility of using these reflexes as hearing tests is conditioned by two circumstances: *a.* that the reflexes be of constant appearance; and *b.* that their threshold be not too high.

That the reflexes appear constantly cannot be doubted because numerous authors have given perfectly consistent descriptions of

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†From the Central Institute for the Deaf and the Dept. of Physiology, Washington University.
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them. Since Politzer[2] had determined that the tensor tympani muscle is innervated by the fifth and the stapedius one by the seventh nerve, and found with a large model of the middle ear that the contractions of the tensor tympani ought to diminish the amplitude of vibrations of the tympanic membrane, numerous authors have observed reflex contractions of this muscle. The literature has been very thoroughly reviewed by Köhler,[3] Kato[4] and again by Schäffer and Giesswein[5] and Mangold,[6] so that we need here only to pay the tribute to the investigators who accomplished the difficult pioneer work by mentioning their names (Hensen, Bockendahl, Pollak, Luca, Hammerschlag, Schapringer, Ostmann, etc.). Since the actual theories on the function of these muscles have already been proposed and discussed by these authors we will have to discuss their work later more in detail.

The paper of Kato is a fundamental one. In it the conditions under which the tensor tympani contracts were studied very thoroughly and besides the reflex of the stapedius muscle was also described as being a constant phenomenon. Kato's statements have been completed recently by Kobrak[7] and Philip.[8] Of special interest is the paper of Lüscher,[9] who has described the stapedius reflex in humans. Later Lüscher[10] reported a second case and Kobrak[11] still another one.

Kato tried to determine the threshold of the reflexes and the upper and lower limits of the tones producing it. With the rabbit he found that the limits are 128 and 50,000 cycles, although occasionally tones of even 64 cycles may elicit the reflexes. For determining the threshold he used tones from *e2* to *a5* produced by whistles, and found that as a rule the higher the tone the lower the threshold, *i. e.*, the higher the tone the less intensity necessary to elicit the reflex; and further that the stapedius reflex always has a lower threshold than that of the tensor tympani. Kato concludes that the stapedius may be brought to reflex contraction with rather weak tones, while the tensor contracts only with very intense tones (loc. cit., p. 623). This conclusion, however, is not granted by the protocols of Kato, which undoubtedly show that rather weak tones are enough to elicit the tensor reflex, but since at that time no easy method was available to measure the intensity of tones, and since this conclusion gave a strong support to the "protection theory," Kato's statement has been generally accepted. However, Lüscher emphasized that the stapedius reflex in humans is produced by tones of intensities that are very frequent in the normal conditions of life.

Kobrak, using a method similar to that of Kato, determined again the threshold of the reflex (tensor tympani) with rabbits and found that the rabbit's ear shows the highest sensitivity in the neighborhood of c4. Kobrak measured the intensity of the tones in terms of m.m. of air pressure in the whistle. Kobrak has since announced

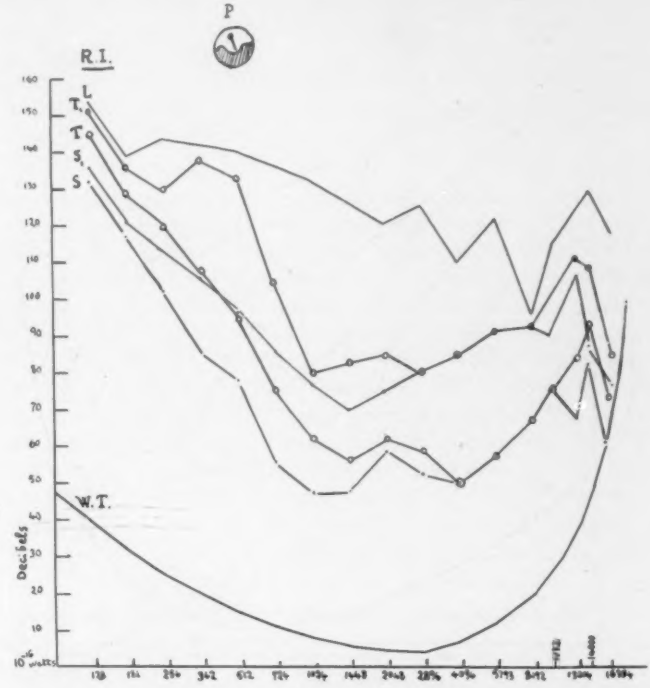

Fig. 1. Threshold curves of the acoustic reflexes of the muscles of the middle ear. Rabbit I. (T) curve of the tensor tympani; (S) curve of the stapedius muscle; (T1, S1) threshold curves after the perforation of the drum membrane was made. (W.T.) the threshold curve of the human ear after Wegel. (L) limit of intensity of the tones produced by our audiometer. The drawing on top of the figure indicates the site and size of the perforation.

the publication of audiometric curves of the stapedius reflex in humans.[11]

The measurements of Kato and Kobrak cannot be considered as totally exact, because as Kobrak himself states, the method used for measuring the tone intensity was not sufficiently reliable, besides Kobrak's and Kato's statements are at some variance from each

other; therefore, it seemed desirable to determine first the threshold of the reflexes, in order to have basis for further experiments.

The experiments have consisted of the determination of the lowest intensity of a tone of long duration (2 to 5 seconds) that is able to set up a visible contraction of the muscles.

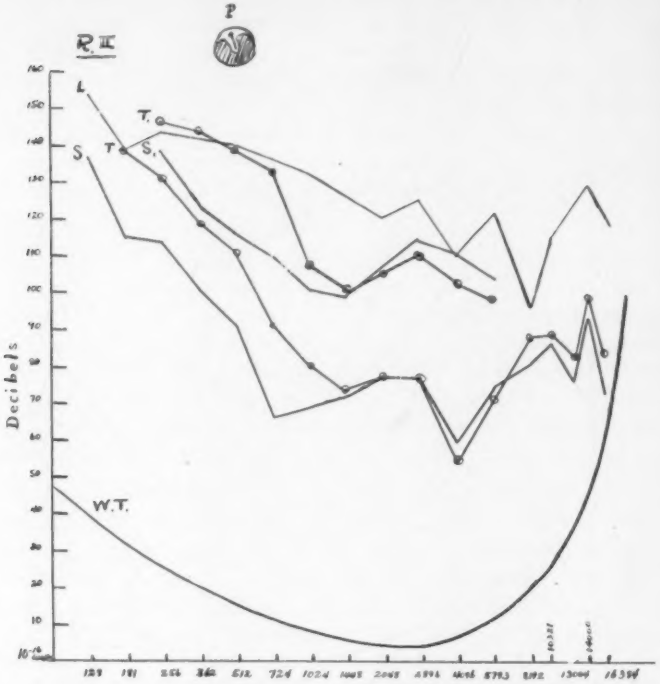

Fig. 2. The same in rabbit II.

Technique: Since in this first series of experiments the problem was to determine the threshold curve of the reflex, *i. e.*, the relation of the pitch to the tone intensity necessary to produce the reflex, only a subjective observation of the reflexes was necessary, because if sufficient magnification is used the onset of the reaction can be determined with enough accuracy.*

*Since no chain is stronger than its weakest link, it is evident that to use a method of absolute exactness for determining the onset of the reflex would not be in proportion with the numerous causes of error in measuring the intensity of the tones conducted to the ear (S. later). The onset of the reflex can be determined with absolute exactness only by means of (a) recording the action potentials of the muscle or its nerve, (b) isometric records of the tension developed by the muscle. Experiments carried out with this last method will be soon described.

The technique is easy: the middle ear is reached in a manner similar to that used in the radical operation on the mastoid bone. The drum membrane and the ossicles (malleus, incus) are extirpated and the contraction of the tensor tympani and the movements of the head of stapes observed under the microscope through the enlarged auditory canal. Since binocular dissecting microscopes do not give enough magnification, an ordinary compound microscope mounted on a special stand has been used. With this microscope any magnification up to 200 can be obtained, but it has been found advisable not to go over 80 to 100, because with higher magnification it is impossible to have both the stapes and the tensor tympani muscle in the field of vision.

The tones are conducted to the other ear. They were produced with a heterodyne audiometer from the Bell Telephone Laboratories. In the beginning it was a serious problem to have a uniform means of conduction of the tones to the ear, because if the pinna is intact, a slight change in its position causes a noticeable change in the threshold of the reflex. In order to work with uniform conditions the pinna has been extirpated and tones conducted by means of a tube to the bony auditory canal. An ebonite funnel is attached to the loud speaker and an ebonite tube passed over the bony canal and fixed in place by means of a clamp attached to the head holder, thus securing the immobility of the tube throughout the experiment. The ebonite funnel and the ebonite tube are then connected by means of a short rubber tube. Repeated control experiments have shown that the threshold of the reflexes slightly changes if the length of the rubber tube varies, even within narrow limits; this may account for the differences in threshold of the different rabbits.

Since the audiometer was calibrated to be used with the earpiece of the loud speaker close to the ear, a new calibration has been made. Four normal ears have been tested, using the conducting system that is used with experimental animals and the mean value of the thresholds considered to be identical to the threshold curve of Wegel.[12] Upon this curve the values given by the audiometer for the rabbit ear have been transposed, thus obtaining the curves reproduced in Figs. 1-5. This procedure, of course, does not give an exact measure of the intensity of the tones, but the obtained figures must be approximately correct. The greatest difficulty with this method consists in the necessity of having a receiver with uniform efficiency. Unfortunately this is not the case with ours. The Western Electric 555 loud speaker, although able to produce very intense tones, does not reproduce all the tones with the same intensity. This can be

corrected for tones of intensities near the threshold by means of testing a certain number of normal ears, but for intense tones the peaks and gaps although much less pronounced will again appear. This undoubtedly is the reason why the curves in Figs. 1-5 in the region 2,000-16,000 cycles show peaks and gaps. Taking into account the peaks in threshold of normal ears in the case of constant electrical input, the assumed curves of Fig. 6 have been drawn.

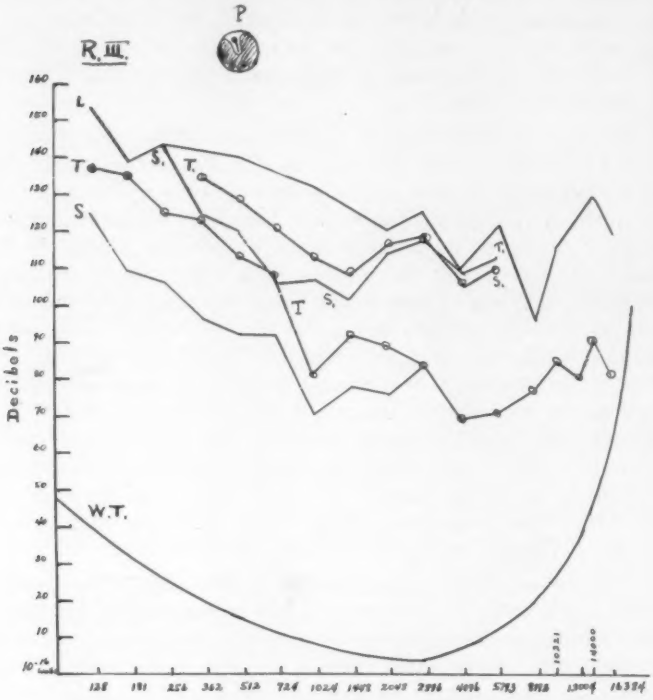

Fig. 3. The same in rabbit III.

The tones have been conducted to the right ear and the observation made on the muscles of the left. Experiments in which the right cochlea was destroyed have shown that the tones reaching the left ear through bone conduction are largely subliminal, therefore it has not been found necessary to extirpate the left cochlea.

Results: If the threshold intensity values are transposed upon the human threshold curve (Wegel), the curves (T) and(S) of Figs.

1-5 are obtained. (T) indicates the threshold of the tensor tympani muscle, (S) that of the stapedius muscle.

The reflexes are produced by tones of sufficient intensity throughout the pitch range 90-100 d.v. to 20,000 d.v. It must be noted, however, that these figures are dependent upon the audiometer and loud speaker. Occasionallp it is possible to elicit reflexes with tones of less than 90 d.v. but the intensity has to be so high that the over-

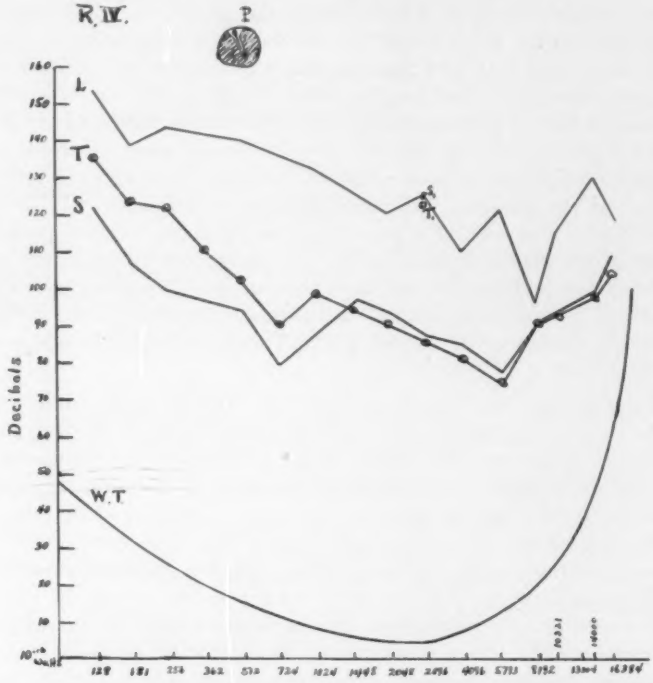

Fig. 4. The same in rabbit IV.

tones in the receiver or transmission system must have such an intensity that they alone might be able to set up the reflex reaction. If the higher limit is tested with the König rods it is found that even tones of 45,000 d.v. are able to produce the reflex.

A striking fact is that the curves have their lowest point at about 2,000 to 4,000 cycles, *i. e.*, lower or higher tones must have a greater intensity (energy) in order to produce the reflex. In this the curves are similar to the human threshold curve, except that in the human

curve there is a very fast ascent of the threshold when the tones come near 12,000 cycles, while in the rabbit curve the ascent seems to be slower.

But undoubtedly the most interesting fact is that the threshold curve of the two muscles do not coincide or run parallel, *i. e.*, that the differences in thresholds of the muscles are dependent upon the pitch. For tones up to 3,000 cycles the stapedius has a lower threshold than the tensor; between 3,000 and 8-10,000 both muscles have the same threshold or in some rabbits that of the tensor tympani is slightly lower; from 10,000 up the stapedius often seem to have again a lower threshold than the tensor tympani. This is a fact of great importance, therefore we stress the point that the technique used justifies the statement that the differences in thresholds of the reflex contractions of the two muscles depend upon the pitch of the tone, *i. e.*, that to each pitch will correspond a different contraction of the muscles. The technique is also sufficiently reliable to determine that the differences in threshold at the various pitches are approximately represented by the differences in the height of the curves in Figs. 1-5, but more accurate determinations, with the help of isometric myographs* are necessary to establish the reflex pattern corresponding to each pitch. These determinations are now being made.

Discussion: The curves (T) and (S) of Fig. 6 show only the threshold of the reflexes but since both the sensation of hearing and the muscle reflexes are brought forth by the activity of the nervous system as a result of cochlear responses to sound stimuli the conclusion is justified that the sensitivity curve of the cochlea† of the rabbit, like that of the human, is not a straight line. The energy of the threshold tones is dependent upon the pitch, the smallest amount of energy required to elicit the reflex corresponding to tones of 2,000 to 4,000 d.v. As we shall see later, this curve does not change its form when the drum membrane is extirpated, which undoubtedly signifies that the differences in sensitivity to tones is not determined by resonance of the drum membrane or by the functions of the middle ear, but rather by the properties of the cochlea or of the nervous system.

That the differences in the thresholds of the two muscles are dependent upon the pitch of the tone seems to indicate that the "pro-

*It would be well to emphasize here that the direct examination of muscles or isotonic recording of their contractions do not give exact data about the activity of the muscles. The only reliable measure of the muscular contraction is that obtained with isometric myographs.

†It would be better to say the hearing mechanism, i. e., cochlea plus hearing centers.

tection" theory is insufficient. According to this theory the contractions of these muscles should have the purpose of protecting the ear against damage by strong tones. However, we shall stress the point that we are not yet making any assumption upon the physiological

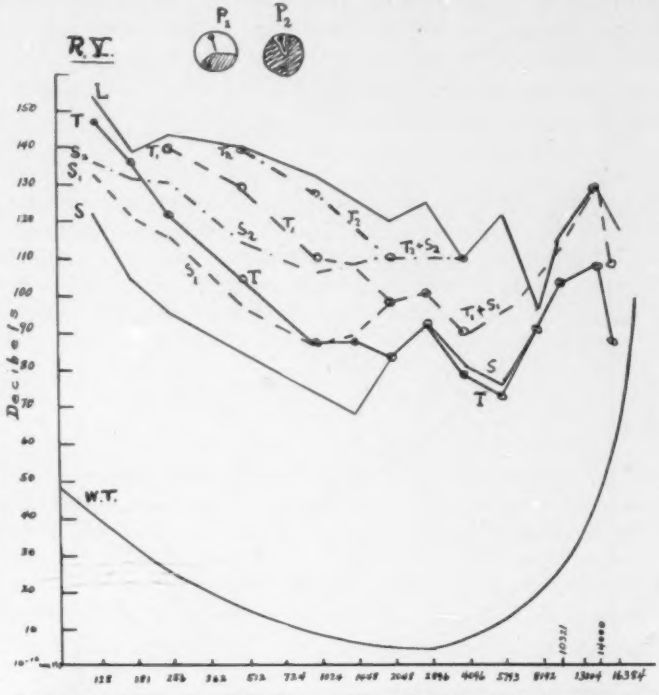

Fig. 5. The same in rabbit V. A small perforation (P1) was first made, after the curves (T1, S1) were obtained the perforation was enlarged to the size indicated in (P2) and the curves (T2, S2) were obtained.

significance of the tensor and stapedius reflexes. Physiological conclusions can be drawn only when the properties of the reflexes are totally known, and we are still very far from this point.

The threshold curve goes through the speech region of the auditory field. Moreover, the difference in thresholds of the two muscles changes completely within this region. This indicates that in the hearing of speech both muscles are constantly active and that the relations of the tensions developed by them will also be changing constantly. The point has already been stressed in the preliminary communication.[1]

II. THE THRESHOLD CURVE AFTER EXTIRPATION OF THE TYMPANIC MEMBRANE.

If in the drum membrane a perforation is made the threshold curve changes according to the site and size of the perforation. An accurate study of the relation between the kind of the perforation and the hearing loss will be made later. In this paper only the results obtained after large perforations will be mentioned.

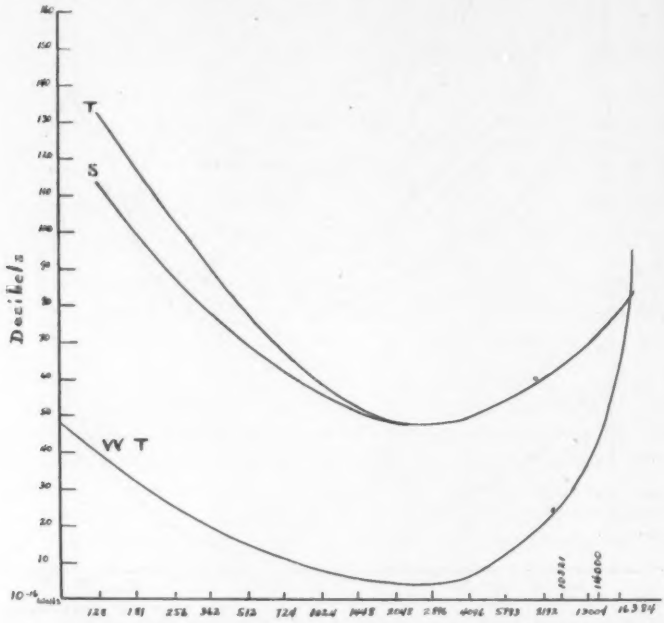

Fig. 6. Assumed curves of the threshold of the reflexes. These curves have been drawn taking into account the curves in Figs. 1-5 and the peaks and gaps of the receiver by constant electrical input. They are, of course, not exact but will indicate general trends of the acoustic reflex field of the rabbit; beyond 16,000 cycles the threshold rises quickly although slower than in a human.

In order not to change the tone conduction the perforation has been made through the ebonite tube attached to the bony canal. The drum membrane has been cut round the malleus but the ossicles have not been touched. The examination of the middle ear after killing the rabbit always has shown that neither a hemorrhage had taken place nor had the ossicles been dislocated, so that the hearing loss must be attributed solely to the lesion in the tympanic membrane.

Results: After total extirpation of the drum membrane a shifting of the threshold curve, in all tones, appears. Our audiometer does not always give tones of sufficient intensity to elicit the reflex after extirpation of the membrane, but an examination of the curves in Figs. 1-5 indicates that the hearing loss must have been approximately the same for every tone (around 20 sensation units). At any rate, it is sure that the hearing loss affects the high tones approximately in the same proportion as the low ones.

Discussion: This result is in disagreement with the classic otological belief that disorders in the transmission apparatus affect chiefly the low tones, while it does not modify the perception of the high tones or at least in much less degree.

However, the necessity of modifying this rule has already been pointed out several times. First by Wien,[13] who in his determination of the sensitivity of the human cochlea found that middle ear diseases produced a hearing loss for high as well as for low tones; he indicated that the examination with tuning forks is not reliable because the tuning forks give tones of much less intensity in the low than in the high range and therefore a slight loss in the low range will be more easily detectable than in the high range. In modern times the audiometer curves of Dean and Bunch,[14] Ruf,[15] Sonntag,[16] etc., have shown that lesions in the middle ear in many cases are accompanied by a shifting of the threshold for all the tones. The clinical observations, however, are made on ears showing complicated lesions and do not allow of stating definite conclusions. Our experiments in which the lesion in the drum membrane has been uncomplicated show that the drum membrane plays very much the same role in the perception of the low and of the high tones. This disagrees with the results of the studies of the physicists (Frank[17]), but it must be borne in mind that to express the problem of the transmission of sound through the middle ear in mathematical terms is extremely difficult, and in the present state of our knowledge it will always be accompanied by a schematization which is likely to mask important facts. We need here only refer to one very important paper of Fowler,[18] who theoretically and experimentally has pointed out several of the facts that have to be considered in the study of the sound transmission through the drum membrane and ossicles. If the view put forward in that paper is considered it is not difficult to understand that the loss of the drum membrane may raise the threshold of every tone.

The results of our experiments seem to be in disagreement with those of Crowe and Hughson,[19] but further work is necessary in order to be able to establish an accurate comparison.

SUMMARY OF CONCLUSIONS.

1. The threshold curve of acoustic reflexes of the muscles of the middle ear in the rabbit bears the same general configuration as the human threshold curve of audition, showing the greatest sensitivity of the hearing mechanism at around 2,000 to 4,000 cycles; but the threshold does not rise as rapidly in the high pitch region as in the human.

2. The curves of the tensor and stapedius do not coincide or run parallel but change their relationships with differences in pitch.

3. After extirpation of the drum membrane there is a very nearly constant loss of sensitivity throughout the whole tone range. This loss is of the order of 20 decibels, but the sensitivity curve remains qualitatively unchanged. This indicates that the highest sensitivity in the area, 2,000-4,000 cycles, is not due to resonance in the drum membrane or middle ear mechanism.

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ANATOMY OF THE EIGHTH NERVE.

III.—General Plan of Structure of the Primary Cochlear Nuclei.

Dr. R. Lorente de No.*

Although the modern physiologists in dealing with the nervous system already speak in terms of impulses set up in single end organs or single motoneurons and conducted by single fibres, the anatomists are still speaking in terms of large bundles of fibres and of "nuclei" composed of thousands of neurons; often even the bundles and nuclei are imperfectly known. The cerebellum is perhaps the best known part of the nervous system and yet, as Strong (1928) in a very suggestive article has recently pointed out, many problems, even fundamental ones, have to be solved before the cerebellum may be incorporated in a functional diagram.

The most urgent need of physiology is a knowledge of the minute structure of the central organs, with exact data on all the fibres that end upon any cell and on all the cells upon which any fibre has synapses. Until this be known the interpretation of physiological experiments will continue to be extremely difficult, if not impossible. If the physiologist has data only on certain anatomically easily demonstrable structures but lacks information about the rest of the elements involved in the establishment of the function being studied, he most likely will be misled to the statement of simple explanations, which at best will prove to be incomplete; often he will be unable to plan his experiments.

If physiology is to be aided by anatomical researches, a return to the kind of research conducted by the old masters, Golgi, Lenhossek, Kölliker, v. Gehuchten, Retzius and, above all, S. R. Cajal, is absolutely necessary. These researches have been extended to the lower vertebrates chiefly by P. Ramón and the schools of Johnston

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and C. J. Herrick, but as to the nervous system of mammals, it can be said that they were practically discontinued when the publication of Cajal's monumental book was finished in 1904. The reason for it lies in the fact that the use of the silver chromate or the mercury methods of Golgi demands special training, which can be obtained only in very few laboratories. However, it is true that only the Golgi methods, or even the more difficult method of Ehrlich, are able to give complete information on the morphology and connections of the nerve cells.

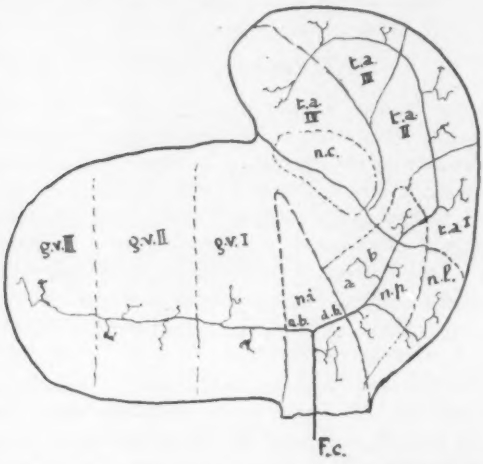


Fig. 1. Showing the approximate position of the different regions of specific structure of the primary acoustic nuclei, projected upon a longitudinal section. Adult cat.

(G.v. I, II, III) Ganglion ventrale with its three regions; (N.i.) Nucleus interstitialis; (N.p a, b, c) Nucleus posterior with its three regions; (N.l) Nucleus lateralis; (T.a., I, II, III, IV) Tuberculum acusticum with its four regions; (N.c.) Nucleus centralis. (F.c.) is a fibre of the cochlear nerve (coming from the central part of the cochlea), which divides in ascending and descending branches (a.b., d.b.), and gives collaterals in all the regions but the N.c.; cells of this nucleus, however, send dendrites upwards, i.e., towards the T.a., where they come in contact with the collaterals of the cochlear fibres. These collaterals are shown in the following illustrations.

The author using these methods in the study of different regions of the nervous system has collected data in the last ten years that may be of interest to physiologists. In this paper some details on the structure of the cochlear nuclei are given.

Technique: The Golgi method as described by Cajal (1894) has been used for staining the nerve fibres and nerve cells in young animals (mice, rats, cats up to fifteen days of age). The dendritic apparatus of the neurons has been stained after Golgi-Cox in adult

brains (mouse, rat, cat, monkey). The general arrangement of the cell bodies and of the bundles of fibres has been examined in series after Nissl, Weigert-Kultchitzky and Cajal. Several hundreds of brains have been used. The material has been prepared and studied from 1922 to 1932.

Results: For historical data and an account of the actual knowledge of the central branch of the cochlear nerve and its nuclei the reader is referred to the work of Cajal (1909), Herrick (1927), Fuse (1913) and Poljak (1932): the details to be described here almost totally have to be added to these descriptions.

The cochlear fibres shortly after their entrance into the medulla divide into ascending or anterior and descending or posterior branches (more details in Lorente de Nó, 1933a). These branches end in the primary cochlear nuclei, which although generally described as having three parts (ganglion ventrale, with subdivision in anterior and posterior part and tuberculum acusticum) in reality have thirteen regions of specific structure (see Fig. 1). Each cochlear fibre establishes contacts with cells of every one of these thirteen regions.

Details of the division of the cochlear fibres can be seen in Fig. 2. The ascending branch is generally a trifle thicker than the descending one; from the fibre itself before it divides or from one of the branches a thin collateral arises, which ramifies itself within the limits of the nucleus interstitialis.

The ascending branch crosses the ganglion ventrale, giving collaterals for its three regions (see Fig. 1, g.v. I, II, III).

The descending branch gives collaterals for the nucleus lateralis (see Fig. 1, n.l.), crosses the three regions (a, b, c) of the nucleus posterioris (n.p., a, b, c, Fig. 1), giving short collaterals in each one; and penetrates in the tuberculum acusticum, where it gives off branches for each one of its four regions (see Fig. 1, t.a., I, II, III, IV). Some of the cells of the nucleus centralis (see Fig. 1, n.c.) send dendrites to the regions II, III and IV of the tuberculum acusticum, where they come in contact with the cochlear fibres.

The ending of the collaterals is different in each of these regions.

Ganglion Ventrale: The study of the endings in the ganglion ventrale will be made in another paper; some details can be found in Cajal's book. Besides the cochlear fibres there exist in the ganglion ventrale endings of centrifugal and association fibres and of short axons.

Nucleus Interstitialis: Each collateral has numerous branches (see Fig. 3) which repeatedly divide into several fibrils; some of

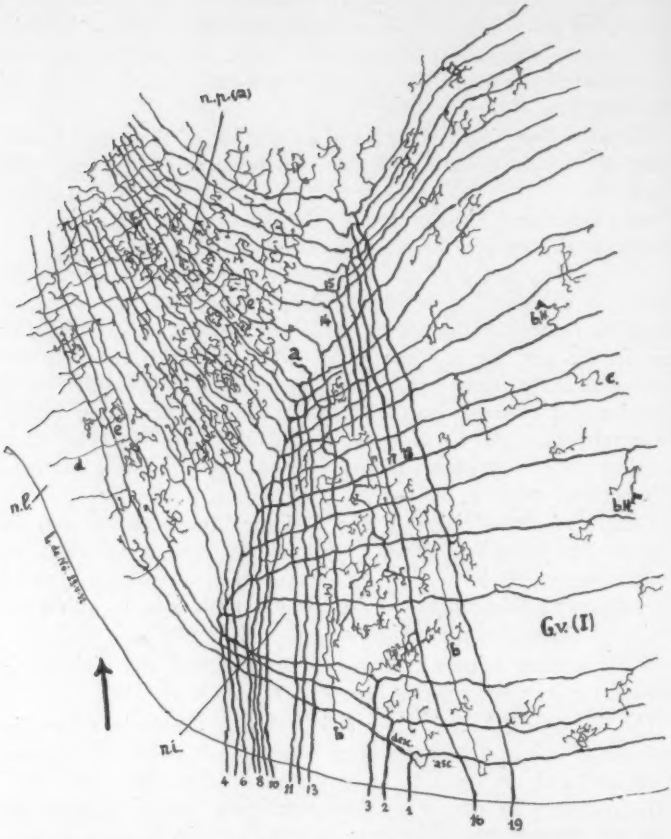


Fig. 2. Longitudinal section through the primary acoustic nuclei of a ten-day-old cat; Method of Golgi. 1-19, fibres of the cochlear nerve; the numerals indicate the regions of the ganglion of Corti from which the fibres are coming; 1 is a fibre from the basal and 19 a fibre from the apical part of the ganglion. The points of division of the fibres are arranged in an arc line of anterior concavity, which is the projection of the axis of an uncoiled ganglion of Corti (Lorente de Nó, 1933a).

(N.l.) Nucleus interstitialis; (G.v.I.) regio I of the ganglion ventrale; (N.p.a.) regio (a) of the nucleus posterior; (N.l.) inferior extremity of the nucleus lateralis. (a) endogenous fibre ramified in the nucleus interstitialis; (b) collaterals of the cochlear fibres for the nucleus interstitialis; (c) collaterals in the ganglion ventrale, which give rise to a diffuse plexus; (b.H.) collaterals that end in a Held bulb; (d) long collaterals (not totally included in the section) for the nucleus lateralis; (e) short collaterals for the nucleus posterior. The arrow indicates the approximate direction of the transversal sections reproduced in Figs. 3, 4, 5, 6, 7, 8 and 12. This drawing, as well as all the others, have been made from a single section, and, therefore, are not ideal reconstructions but actual reproductions of histological preparations. All have been made with the help of the projection apparatus.

the terminal fibrils like (h) and (g) are destined to come in contact with the bodies of the cells; others like (i, k, j) establish contacts with the dendrites. The fibrils that end upon the bodies of the cells form baskets of very narrow meshes; Fig. 3 (h, e, f, b, a) reproduces several baskets which seem to be of different complication, because only a part of the fibres were stained; when all the fibres are stained the baskets are all like that one reproduced in Fig. 3 (a). Between the baskets there is a diffuse plexus (see Fig. 3, pl), which is con-

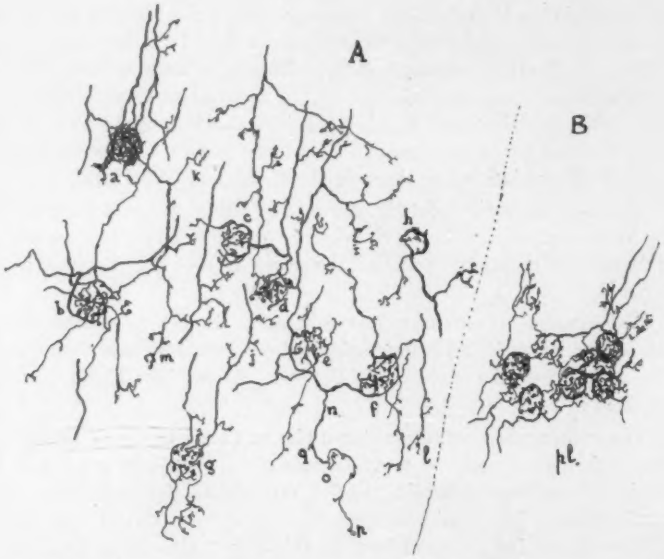


Fig. 3. Details of the endings of the collaterals from the cochlear fibres in the nucleus interstitialis. Ten-day-old cat, Golgi method. (A) from a preparation in which only a short number of fibres were stained; (B) from another preparation in which the stain was more complete. (a, b, c, d, e, f, g, h, l) pericellular baskets (terminal synapses) in which a different number of fibres were stained and, therefore, show an apparently different complication; (j, k, l, m) collaterals for the diffuse plexus (collateral synapses). In this nucleus a fibre (n) builds at the same time terminal synapses (o) and collateral synapses (p, q, r). In (B) the total plexus (pl) (baskets + diffuse intercellular plexus) is seen.

stituted of fibrils establishing connections with dendrites or fibrils going from one basket to another. As Fig. 3 shows, a single fibre may take part in the formation of several baskets.

In addition to the endings of the cochlear fibres still another kind of terminal fibres have been found in the nucleus interstitialis. They are rather coarse fibres (see Fig. 2, a) which give rise to a diffuse

end ramification. It has been impossible as yet to determine the origin of these fibres, but there is no doubt that there are either short axons of a hitherto unknown type of cells or else centrifugal fibres. I rather favor the first alternative.

Cells of the nucleus interstitialis have been reproduced in Fig. 12; they are of two kinds with quite different protoplasmic apparatus.

Nucleus Posterioris: In the posterior nucleus several regions (n.p., a, b, c, Fig. 1) with special neurons must be considered; the protoplasmic (see Fig. 12) and the fibrilar plexuses (see Fig. 5) are quite different in each region. A complete description cannot be given here. Fig. 4 reproduces some collaterals found in the regio (b). Their distribution, although rather diffuse, is more circumscribed than in the nucleus interstitialis; in (a) a collateral establishing contact with dendrites and in (b, c, d) pericellular baskets have been drawn. Besides the cochlear fibres, there are in the nucleus posterioris other kinds of endings—endogenous and centrifugal.

Nucleus Lateralis (see Fig. 12, n.l.): This nucleus is innervated by long collaterals of the cochlear fibres (see Fig. 5); it is apparently a highly differentiated part of the regio (a) of the nucleus posterioris.

Tuberculum Acusticum: The descending branch of the cochlear fibres has an arciform course within the tuberculum acusticum and during it gives off collaterals for its four regions (see Fig. 1, t.a., I, II, III, IV).

The collaterals constitute a dense plexus (see Fig. 6) which occupies only layers 2 and 3; no collaterals are found in layers 1 and 4 or in the nucleus centralis. Fig. 7 reproduces details of the end ramifications; here again we find baskets for the bodies and more diffuse plexus for the dendrites. In this Fig. 7 also the general plan of structures of the regio I is indicated; Fig. 12 contains several types of cells with dendritic apparatus of the regio I; Fig. 10 some cells with stained axons of the regio II.

The tuberculum acusticum, like the other mentioned regions, still receives other kinds of afferents.

These are first centrifugal fibres, which form a large hitherto undescribed bundle of fibres (see Fig. 8) which arrive through the caudal stream of the trapezoid body, pass between the descending trigeminal root and the ganglion ventrale or the nucleus posterioris and penetrate into the tuberculum acusticum through the nucleus centralis without leaving a single collateral in it (see Figs. 8 and 9). The centrifugal fibres end in a very similar manner as the cochlear ones (see Figs. 7 and 8).

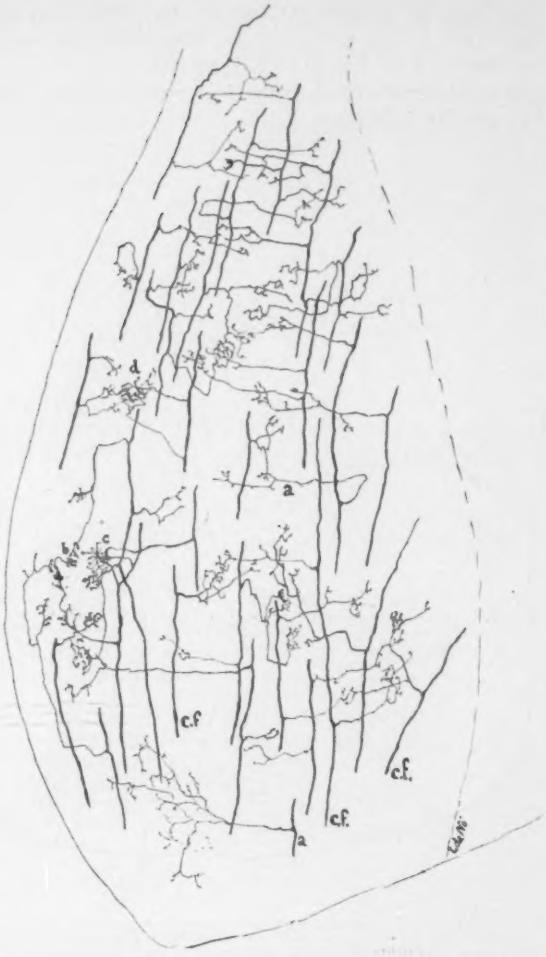


Fig. 4. Details of the collaterals ending in the regio (b) of the nucleus posterior. Transversal section. Method of Golgi; seven-day-old cat. (C.f.) cochlear fibres; (a, a) collaterals for the diffuse plexus; (b, c, d) pericellular baskets. In this region of the nucleus the innervation of the cells is more differentiated than in regio (c) or in the nucleus interstitialis.

Another powerful, also undescribed, stream of fibres reaches the tuberculum acusticum, entering through regio IV (see Fig. 11, a.f.). They are myelinated, medium size and thin fibres which end in layers 3 and 4. It is noteworthy that this stream of endogenous fibres

has fibres from the ganglion ventrale for the tuberculum acusticum (see Fig. 10, a.f. 1) and fibres from the tuberculum acusticum for the ganglion ventrale (see Fig. 10, a.f. 2 and 3).

The main differences between the four regions of the tuberculum acusticum are the following:

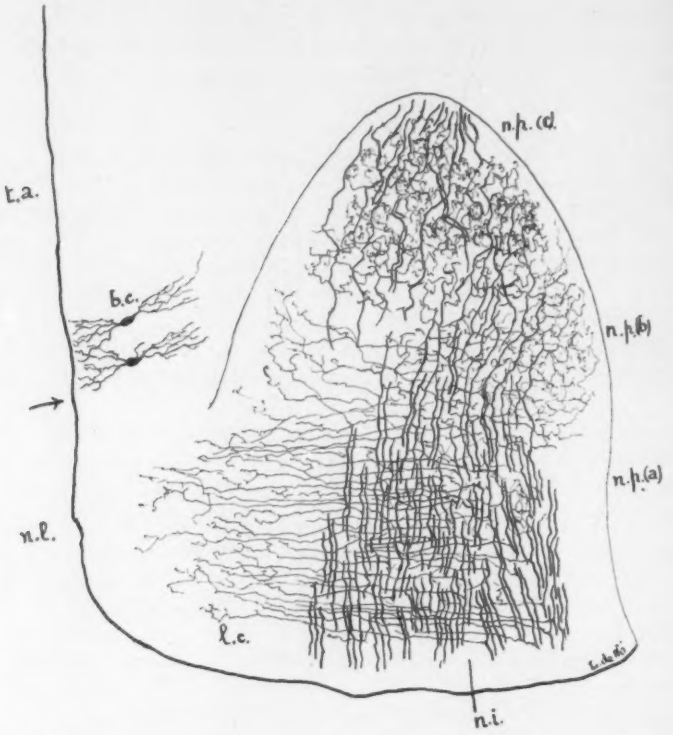


Fig. 5. Transversal section through the nucleus posterior, nucleus lateralis and tuberculum acusticum. Method of Golgi. The drawing has been made at very low magnification and, therefore, is half-diagrammatic. (N.i.) nucleus interstitialis; (N.p., a, b, c) nucleus posterior with its three regions. (N.l.) nucleus lateralis, receiving long collaterals, (l.c.); (T.a.) tuberculum acusticum with two bipolar cells (b.c.) of the second layer. The arrow marks the limit between nucleus lateralis and tuberculum acusticum.

This section passes very approximately through the same plane as the section reproduced in Fig. 12; the comparison of both illustrations readily shows the close correspondence of protoplasmic and fibrilar plexuses.

Regio I receives many afferents and less centrifugal fibres and still less association fibres; no part of the nucleus centralis is attached to it.

Regios II and III have a part of the nucleus centralis attached to them and receive as many afferent as centrifugal and association

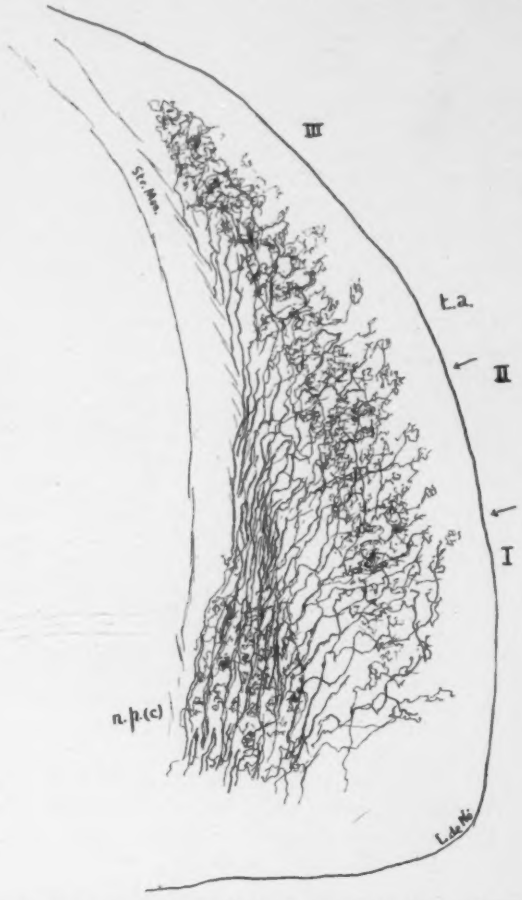


Fig. 6. Endings from the cochlear fibres in the tuberculum acusticum (t.a.), and collateral plexus in the region (c) of the nucleus posterior. Twelve-day-old cat; Golgi method; transversal section. Details of the endings in the region inclosed between both arrows are shown in Fig. 7.

fibres; Regio II has a well developed layer 3; Regio III is lacking in it.

Regio IV has a much simpler structure than the other three regions and receives chiefly association fibres.

Nucleus Centralis: The nucleus centralis, which from certain points of view can be considered as a fifth layer of regios II and III of the tuberculum acusticum, contains the largest cells of the primary acoustic nuclei, which are of two types—some have ascending dendrites which penetrate the tuberculum acusticum and some others have only dendrites that remain within the boundaries of the nucleus, and therefore can be brought to discharge only as a consequence of the activity of the other cells of the acoustic nuclei. The position of the nucleus centralis which also contains cells with short axis cylinders is indicated in Figs. 1 and 8.

Discussion: This survey of the elements of the first central station of the cochlear fibres, although very fragmentary, already shows that we have to do with structures of much higher complication than is generally assumed. The cochlear nuclei appear now to be even more complicated than the retina or olfactory bulb, which are, according to Cajal's description, the primary nuclei of highest differentiation in the nervous system. Each cochlear fibre has connections with very numerous cells grouped in no less than thirteen regions of specific structure in which different types of neurons are found. In this paper data on a few of the cell types have been given and a glance at the accompanying illustrations (see especially Fig. 12) show that the differences between them are really considerable. Although numerical data are not yet available, it is already safe to state that in the primary cochlear nuclei no less than forty or fifty types of neurons are present, and that each cochlear fibre establishes connections with many hundreds, perhaps thousands of cells.

This state of things is by no means peculiar to the cochlear nerve. Any other sensory nerve, be it cranial or spinal, has similar central distribution; with the spinal nerves or their cranial analogies, the trigeminus, the picture is even more complicated because they contain fibres of many different categories. The author, however, was able to differentiate in the primary trigeminal station (Lorente de Nó, 1924) several systems pertaining to different classes of sensibility.* and to demonstrate that each fibre from each system has connections with several nuclei in the same way as the cochlear fibres do.

*At first sight this statement seems to refer to an extremely difficult piece of work, demanding the most delicate experimental analysis; however, it refers to a relatively easy research. On one hand the fields innervated by the trigeminal nerve are partly common to other nerves (facialis, glossopharyngeus, vagus, first cervical nerves), and on the other hand to the trigeminal system belong several reflex apparati (masticatory muscles, muscles of the eye, muscles of the tongue, facial muscles, muscles of the middle and external ear, etc.). It is now evident that a nucleus common, for instance, to the V and IX nerves cannot receive fibres innervating the eyelids but must necessarily receive fibres of the common field (mouth) and that a trigeminal nucleus giving rise to a pathway connecting it with the motor nuclei of the muscles of the jaw must necessarily belong to fibres innervating the receptive field of masticatory reflexes, etc. Therefore, if the relation of the trigeminal system with other sensory and motor systems are carefully studied it becomes easy to ascertain the physiological role of the different nuclei and pathways.

The cochlea (see discussion in Lorente de Nó, 1933a) receives several kinds of fibres with specific distribution. It was, therefore, to be expected that several categories of fibres be found in the central cochlear branch. However, repeated examinations have consistently failed to demonstrate fibres other than those represented in Fig. 2. The evidence, however, is not conclusive and I do not think the question is settled. It is true that hundreds of brains have been examined, but it is also true that the differences may be apparently

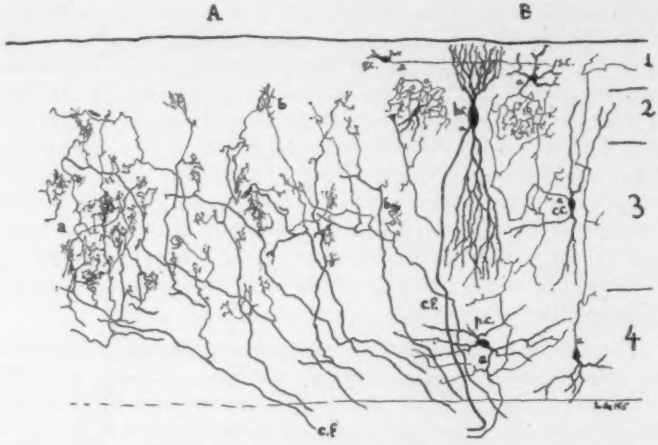


Fig. 7. In (A) details of the endings of the collaterals of the cochlear fibres in the tuberculum acusticum; same preparation as in Fig. 6. In (B) composite, half-diagrammatic picture showing the fundamental plan of structure of the tuberculum acusticum. (In each layer only one or two types of cells have been included.) (1, 2, 3, 4) the four fundamental layers; (g.c.) granule cells; (s.c.) star cells; (b.c.) bipolar cells; (f.c.) fusiform cells; (c.c.) corn cells; (p.c.) polimorf cells; (a.a.c.) ascending axon cells. The axon is marked with (a); (c.f) cochlear fibres with their collaterals, which form pericellular baskets (b) and diffuse plexus (a). Note that neither the cells of layer 1 nor the cells of layer 4 are in contact with the cochlear fibres; the plexus is formed only in layers 2 and 3.

slight and have, therefore, escaped my analysis. If it is considered that the fibres from the cristae and maculae of the labyrinth have similar distribution in the nuclei of the floor of the fourth ventricle, the differences being slight (Lorente de Nó, 1933a, b) it becomes evident that the cochlear fibres must show still slighter differences.

The cells of the primary nuclei may be divided into classes according to several points of view; each division has special physiological significance.

The first division is into cells with short and cells with long axis cylinder. The cells with long axis cylinder set up impulses which

are carried to higher nuclei through the secondary pathways; they may be called efferent cells; but the impulses set up by the cells with short axis cylinder do not leave the boundaries of the primary nuclei; they circulate through them and at the end impinge upon the cells with long axis cylinder. Therefore, the discharge of the efferent cells will be dependent on two factors: the afferent cochlear impulses and the impulses set up in the cells with short axis cylinder. This is why it would be convenient to call this last class of cells "regulator neurons." The names intercalary (Schaltzellen) or internuncial neurons are misleading because the cells with short axis cylinder are not arranged in series between the afferent fibres and effector cells but in parallel chains superimposed on the shortest pathway [Cajal (1911); Herrick (1927); Lorente de Nó (1932b)]. The existence of regulator cells establishes a fundamental difference between the peripheral and the central synapses. The neuromuscular junction, for instance, is a dead-beat synapse that within the limits of refractory period transmits to the muscle every impulse it receives through the nerve fibre. The central synapse, however, is a "selective" synapse and the transmission of the afferent impulses will be dependent on the function of the cells with short axis cylinder (further discussion below).

The secondary pathways from the primary cochlear nuclei form three well known bundles of fibres: the trapezoid body, the striae of Held and the striae of Monakow. The literature contains conflicting data about the origin of these pathways, but according to my preparations, the origin of each one is the following: trapezoid body — ganglion ventrale + nucleus interstitialis; Held striae, n. posterioris; Monakow striae — tuberculum acusticum + nucleus centralis. Taking into account that the nucleus interstitialis and the nucleus posterioris have the simplest structure, one is inclined to think that the Held striae constitute the main reflex pathway, while the other paths chiefly conduct impulses giving rise to acoustic sensations. However, there are facts that decidedly speak against this schematic view; first, the anatomy of the cochlear paths, and second, the physiological properties of some acoustic reflexes. The anatomy teaches us that there are perhaps fibres that go from the primary nuclei to the internal geniculate body without first giving collaterals to the medulla and midbrain, but also that fibres coming from every one of the primary nuclei give collaterals in the system: oliva superior complex + nuclei of the lateral lemniscus + posterior colliculus; since this system has connections with motor nuclei, its reflex function cannot be denied. On the other hand, it has been found

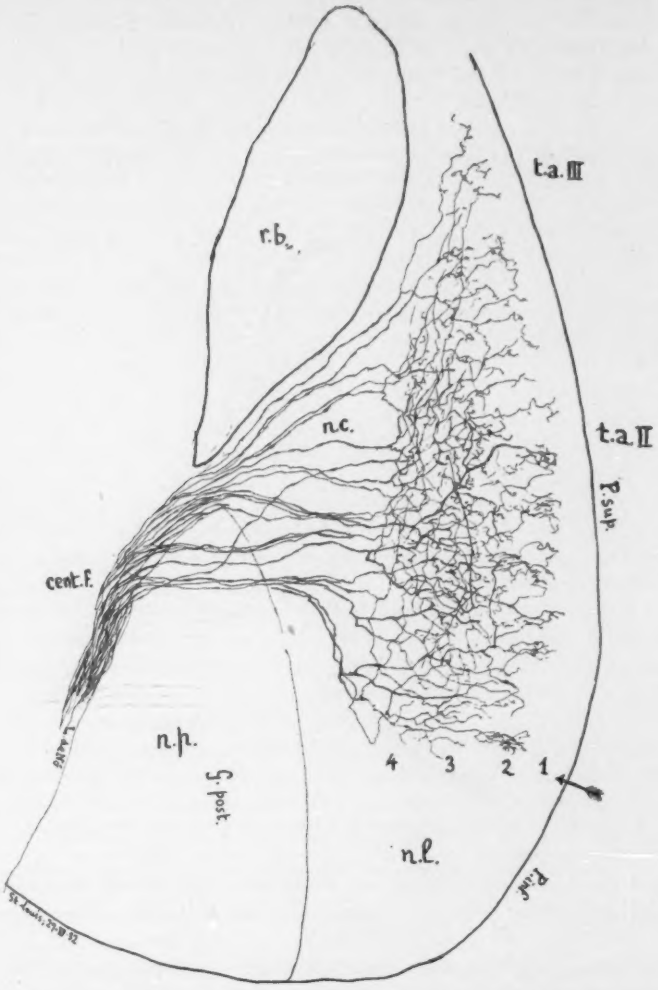


Fig. 8. The centrifugal fibres of the tuberculum acusticum. Twelve-day-old cat, Golgi method, transversal section. (T.a., II and III) Regios II and III of the tuberculum acusticum; (1, 2, 3, 4) the four fundamental layers of this nucleus, in regio III, layer 3, is missing. (N.l.) nucleus lateralis; (n.p.) nucleus posterior; (n.c.) nucleus centralis; (r.b.) restiform body; (cent. f.) bundle of centrifugal fibres, ending in layers 3 and 2 of the tuberculum acusticum. The n.c. does not receive collaterals, neither does layer 4; the fibres are still myelinated while passing these structures, so that they may not establish collateral synapses.

that the acoustic reflexes of the muscles of the middle ear have many properties in common with the acoustic sensations (Lorente de Nó and Harris, 1933). Fortunately, this problem is easily accessible to experimentation and the author hopes to be able soon to offer more conclusive evidence.

If the synapses are studied, another classification of the cells can be made. It has been proposed (Lorente de Nó, 1932b) to classify

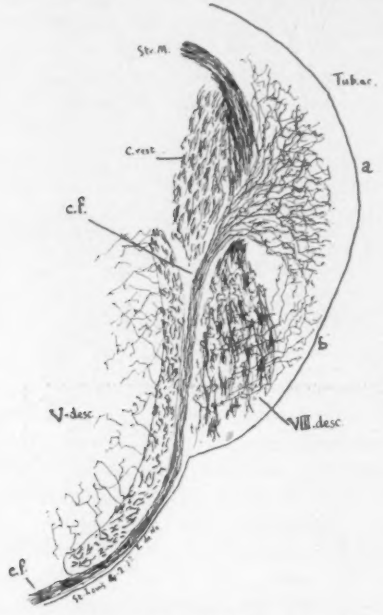


Fig. 9. Cross section through the medulla of a six-day old mouse, showing the course of the centrifugal fibres for the tuberculum acusticum. Method of Golgi.

V. desc.—descending root of the trigeminal nerve; VIII desc.—descending root of the cochlear nerve; C. rest.—restiforme body; Str. M.—Monakow's striae; c.f.—centrifugal fibres; Tub. ac.—a, tuberculum acusticum; b, nucleus lateralis, receiving collaterals from the descending branch of the cochlear nerve, but no centrifugal fibres.

the synapses as "terminal" and "collateral" ones. The terminal synapse is formed when a fibre ends upon the cell body or upon the origin of the dendrites, *i. e.*, on regions of the neuron having Nissl bodies; the fibre, undivided or divided in several branches, forms one or several boutons terminaux of the classic (Auerbach boutons) or of modified type (Held bulbs in the cochlear nuclei, Cajal climbing and mossy fibres and baskets in the cerebellum, etc.). The "col-

lateral" synapses are found on the dendrites. Sometimes the fibre has a very short branch ending upon the dendrite, but more frequently it shows only a small thickening applied to the dendrite; the fibre goes further, establishes other collateral synapses and ends upon a dendrite, or exceptionally, upon a cell body. The terminal synapses have neurofibrillar structure and, therefore, can be stained in favorable cases by means of reduced silver methods; but the collateral synapses that lack the neurofibrillar frame can be stained only by means of Golgi or Ehrlich methods. The terminal synapses on a cell may be outnumbered by the collateral synapses many times, especially in the case of large multipolar neurons.

Examples of collateral and terminal synapses have been mentioned before (see Figs. 3, 4 and 7), but a better example is found in the ganglion ventrale (see Fig. 2). As Held and Cajal described them, the ascending cochlear branches have two kinds of collaterals, thick ones that form the Held bulbs and thin ones that give rise to a diffuse plexus. The Held bulbs apply themselves upon the bodies of a special type of neuron, while the thin collaterals establish synapses on the dendrites of other cells of the same and upon bodies and dendrites of other hitherto undescribed types of cells. This is the most frequent case. A fibre gives off collaterals which establish both kinds of synapses, but there are cases in which the fibre establishes only collateral (for instance, the axons of the dwarf cells of the first layer of the tuberculum acusticum [see Figs. 7 and 10]) or only terminal synapses (for instance, the axons of the Cajal's basket cells of the cerebellum). In the tuberculum acusticum the small stellate cells of layer 1 form presumably only terminal synapses.

It is important to recognize that each type of cell has a characteristic set of synapses. As far as I can see, there is no cell in the cochlear nuclei; and presumably not in the whole central nervous system having less than two kinds of afferent fibres. In the acoustic nuclei the simplest case is that of the cells in the nucleus interstitialis; the most complicated that of the large bipolar cells of the second layer of the tuberculum acusticum where the following main kinds of synapses are found (see Fig. 7): *1*. synapses with the afferent cochlear fibres, on the body and on the descending dendrites; *2*. synapses with the axons of granules of layer 1, on the ascending dendrites; *3*. synapses with the cells with short axon of the second layer, on the body and ascending dendrites; *4*. synapses with cells with short axis cylinder of layer 3, on the descending dendrites; *5*. synapses with cells with ascending axis cylinder on layer 4, on the descending and ascending dendrites; *6*. synapses with the centrifugal fibres, on the body and the descending dendrites; *7*. synapses

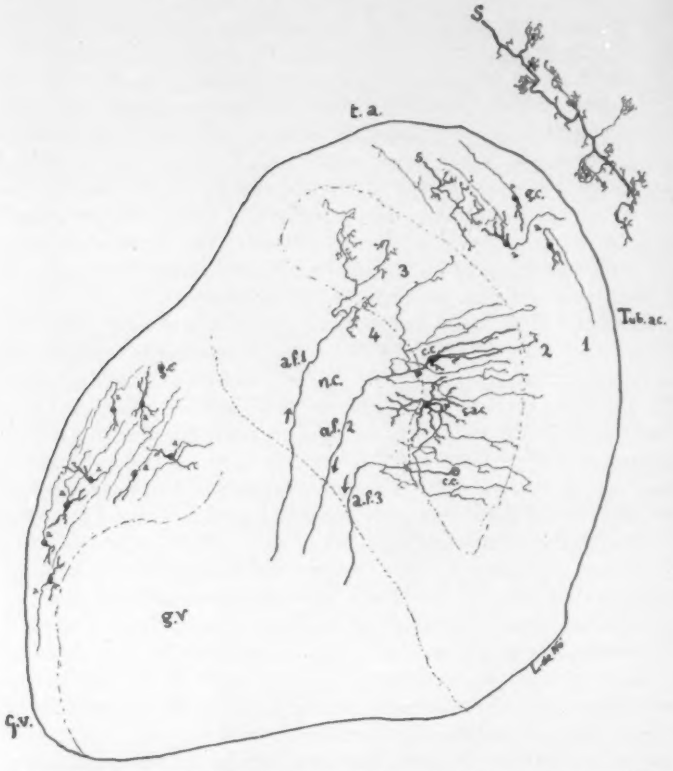


Fig. 10. Structural details of ganglion ventrale and tuberculum acusticum (regio II). (1, 2, 3, 4) the four fundamental layers of the tuberculum acusticum. (g.c.) granule cells of the first layer; (S) an endogenous fibre (short axon) ending in the first layer; this fibre has been drawn with higher magnification on top of the figure (S). (C.c.) are two corn cells of the 3rd layer with axon going towards the ganglion ventrale (association fibres, a.f.2 and a.f.3). These axons give first recurrent collaterals for the same layer (3). The cells giving rise to fibre (a.f.2) has been drawn complete; but of the cell giving rise to fibre (a.f.3) only the contours of the body and the origin of the recurrent collaterals have been indicated, in order not to complicate the picture and make easy the examination of the ramification of the short axon of cell (s.a.c.) (short axon cell) of layer 3. The axons have been marked with (a.) (N.c.) nucleus centralis. (a.f.1) association fibre from the ganglion ventrale to the tuberculum acusticum ramified in layers 3 and 4. (G.v.) Ganglion ventrale with the layer of granule cells of the regio II.

Longitudinal section; fourteen-day-old cat; Golgi method.

with the endogenous association fibres, on the descending dendrites. Since in each of the classes 2, 3, 4, 5 and 7 several types of fibres are included, it is safe to state that the cells in question receive synapses (several hundreds of them) of more than twelve categories; each class of synapses on a special region of the cell. In the

cerebral cortex of the mouse the large deep pyramids will receive at least thirty or forty kinds of synapses (Lorente de Nó, 1922, 1932b). Between both extremes all gradations are present.

This arrangement seems to have an easy interpretation. Independent of any theory on the transmission of impulses from fibres

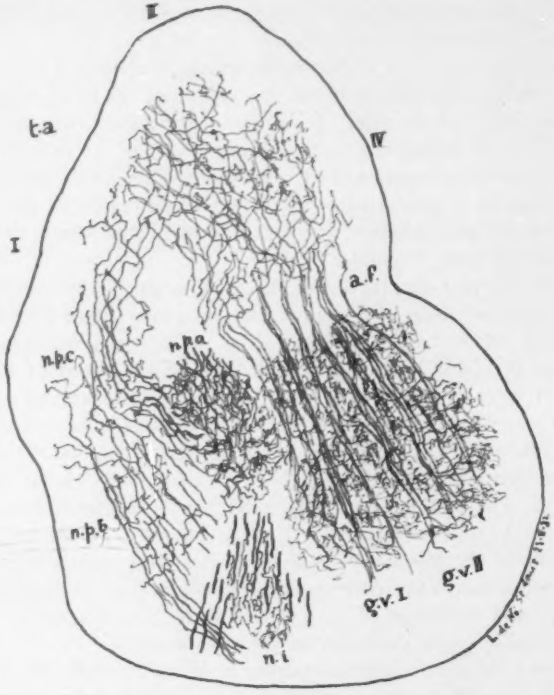


Fig. 11. Longitudinal (very lateral) section through the acustic nuclei of a ten-day-old cat. Golgi method. (This figure and Fig. 1 in Lorente de Nó, 1933a, show half-diagrammatically the afferent systems of the tuberculum acusticum.) (N.i.) nucleus interstitialis with the cochlearis root fibres; (N.p.) nucleus posterior with (a, b, c) its three regions; (T.a.) tuberculum acusticum with regios I, II and IV; (G.v.) ganglion ventrale with regios I and II. The association fibres (a.f.) pass from (g.v.) to (t.a.) and reciprocally; they enter and leave the (t.a.) through regio IV.

to neurons, it can be accepted that a neuron will become excited above threshold when a sufficient number of impulses arrive at it. When a fibre divides, the impulses go into every branch, thus becoming multiplied by the number of branches. Thus, when a fibre gives rise to five boutons terminaux applied on the same neuron, this cell will receive five times as many impulses as the fibre is conducting.

Therefore, when a cell has only synapses with a small number of fibres which give rise, each, to several synapses, the cell will soon receive sufficient number of impulses and reach threshold excitation. But when a cell like the large cells of the second layer of the tuberculum acusticum has synapses with many fibres of many different kinds and each fibre gives rise to only few synapses, that cell will have a higher threshold because many fibres must discharge in order to bring forth threshold excitation.

According to this view the single neuron is already a summation or correlation apparatus because its excitation will be the result of different kinds of impulses. It is now evident that when the function of central nuclei is considered, every one of its cells must be analyzed, because every type of cell, owing to its special set of synapses, must have special value and it must be emphasized that often the synapses with afferent fibres are outnumbered many times by the synapses with "regulator" cells.

Finally another subdivision of the cells in the highly complicated nuclei must be made. *1*. Some cells have a contact with the afferent fibres; *2*. others have no contact at all with them, but only with axons of regulator cells or with collaterals of the axons of efferent cells. In class 2 there are cells with short axis cylinder (regulator), as well as cells with long axis cylinders (efferent cells). Examples in the tuberculum acusticum are, among others, the dwarf cells of the first layer and some cells of the fourth layer and of the nucleus centralis. The discharge of these cells must necessarily be due to impulses set up in cells of the first class. Therefore, if the potentials developed by the axons are recorded at least two main waves must be found, a first wave corresponding to the arrival of the afferent impulses and discharge of the cells of class 1, and a second wave corresponding to the discharge of cells of class 2.

In order to give to this discussion a didactic value, the general traits of the path cochlea-cerebral cortex will be briefly commented upon.

The shortest paths between periphery and cerebral cortex were described by Cajal in a series of diagrams that have become so widely accepted that they begin to be reproduced even without mentioning Cajal's name. In the diagrams a dead-beat character is implicitly assumed for the central synapse and in each successive station only one neuron is considered. According to this view, there are always at least three neurons between periphery and cortex. But if it is considered that all the central nuclei have a complicated structure we must think of ideal selective synapses, rather than of single-cell-synapses. The selective synapses, although physiologically

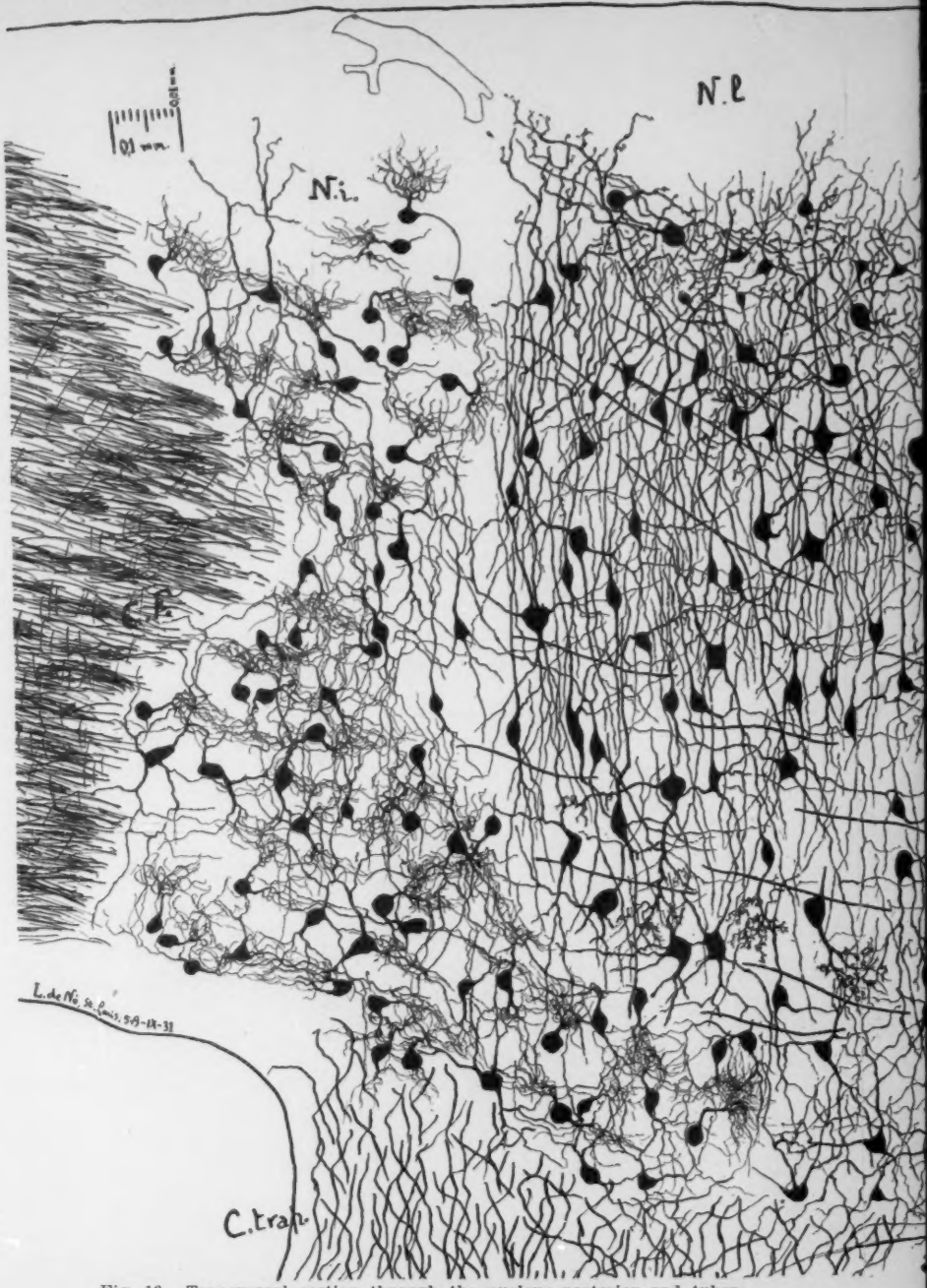
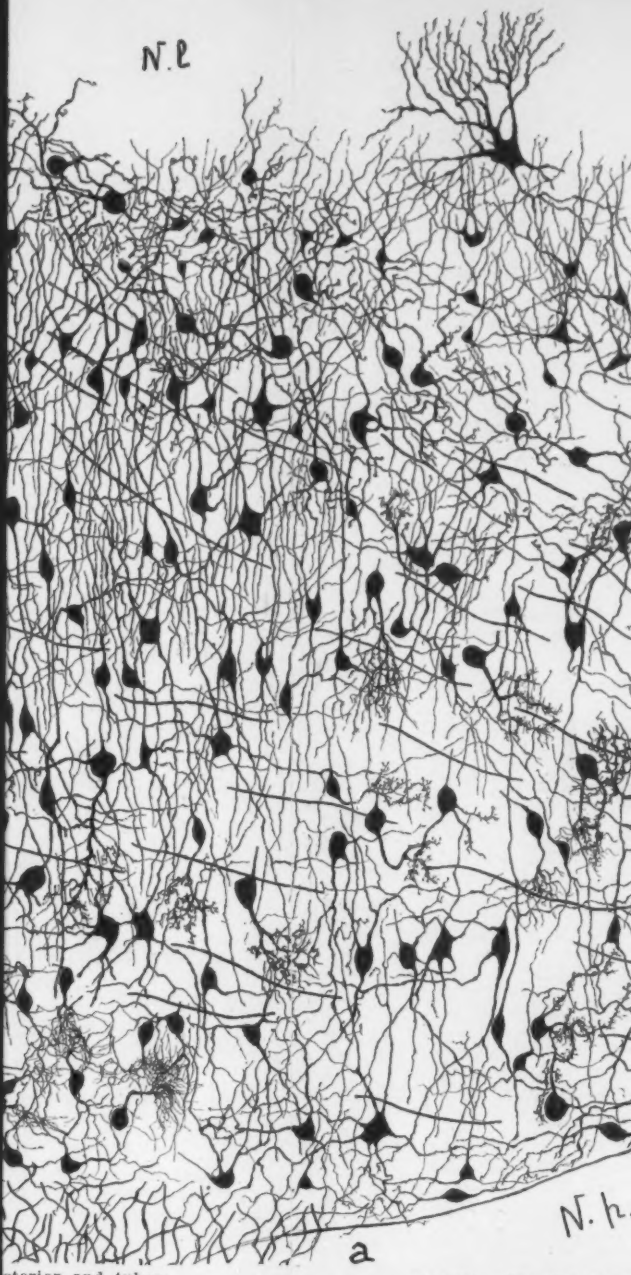


Fig. 12. Transversal section through the nucleus posterior and tuberculum acusticum. Adult cat. Golgi-Cox method.

The drawing has been made from a single section with help of the projection apparatus and every cell has been reproduced with utmost care.

This figure is intended to give an exact idea of the protoplasmic plexus; however, it must be considered that approximately only 1/4 or 1/5 of the cells were stained and, therefore, the drawn plexus is still too simple.

(N.i.) nucleus interstitialis; (N.p., a, b, c) nucleus posterior with its three regions; (N.l.,) nucleus lateralis, of which only the deep layer contained



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ethod in adult brains stains only protoplasmic processes, not contain terminal fibrils or collaterals; except a few d) cochlear fibres (C.F.) below the nucleus interstitialis s posterior.

ination of the figure is sufficient to observe the presence of cells, of which a complete description will be given

a unit, anatomically are an aggregate of numerous cells. Taking now into account the selective character of the central synapse we can give the diagram of Fig. 13. The peripheral organ P.O. is connected with the primary nuclei P.N. by the ganglionic cells. The primary nuclei are connected with the thalamic nuclei (internal geniculate body, etc.) by another direct path, finally the thalamic nuclei are connected with the cerebral cortex (C.C.) by a third

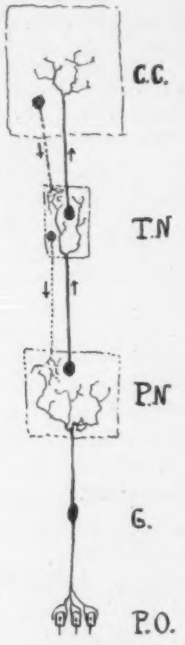

Fig. 13. Explanation in text. The paths in broken lines are centrifugal fibres.

direct path. The synapses as well in P.N. as in T.N. are selective synapses, but of different complication. P.N. is a highly selective synapse having the characteristics described in this paper, but T.N. is much simpler. The cells with short axis cylinder are of only one or two types, and all the efferent cells come in contact with the afferent fibres, *i. e.*, the number of kinds of individual synapses is very low and besides each fibre establishes many synapses on a cell; pre-

sumably the role of the T.N. selective synapse will be more that of summation and concentration of impulses than of differentiation between impulses; it will be more dead-beat than the P.N. synapse. The cerebral cortex is again a highly sensitive synapse, of which systematic description have been given by Cajal (1898-1904) and the author (1922, 1932b).

The interpretation of the anatomical structures given in this paper could be much more complete if data about two fundamental phenomena were available, the transmission of impulses across the synapse and the conduction in the dendrites.

While Forbes, Davis and Lambert (1930) have considered conduction in the dendrites to be similar to that in the axons, Adrian (1930) has recently advocated a different kind of transmission involving the production of slow potential waves. A glance at Fig. 12, however, shows that such waves might as well be produced by summation of potentials of known type. If, in the dendrites, potentials are developed they will be recorded as summated waves of smooth contours because the impulses necessarily must reach them slightly out of phase. This possibility has already been considered by Adrian himself. To have observed the slow potential waves in the nervous system of insects is not a simplification but rather a considerable complication of the problem. The nervous system of insects offers structures of a complication that we are not used to finding in mammals. Cajal, who has dedicated important papers to the study of the retina in invertebrates (1916, 1917, 1918) states that if the retina of insects be compared to a delicate watch, that of the vertebrates has to be compared to a tower clock.

Similar potential waves have been described among others by Berger (1931), M. H. Fischer (1932), Bishop and Bartley (1932) and Gasser and Graham (1932). The last-named authors who have studied the transmission of impulses through the spinal cord relate the slow potential changes with the c.e.s. of Sherrington (1925, Eccles and Sherrington, 1931). I think this is a perfectly justified view. As Gasser and Graham point out, the concept of c.e.s. is now the center of attention of the neurophysiological research and I think with these authors that our ideas will become clear only when the properties of the c.e.s. defined by Sherrington and his school in a series of fascinating experiments can be expressed in terms of the properties of the individual cells and synapses. The reflex arc includes a selective synapse made up of many kinds of cells (Lorente de Nó, 1932c); the concept of c.e.s. undoubtedly refers to the total selective synapse.

To finish this discussion the author feels himself obliged to make an observation. The concepts developed in this and his recent papers are the result of several years work, during which his ideas have, of course, been influenced by the publications of other authors. It is, therefore, impossible to state how much of the theoretical discussion is original or a development of foreign ideas. For instance, the concept of neuron threshold and of the regulating role of the cells with short axis cylinders was mentioned in my note book of the year 1923-24 when I was studying the primary trigeminal nuclei; at that time this concept was a very risky hypothesis; the recent advances of physiology make it almost self-evident, and help to state it in precise form. Therefore, it is well that I mention the names of the authors in whose writings I have found great help in working out theoretical conceptions. They are S. R. Cajal and C. J. Herrick among the neuroanatomists and Sir C. S. Sherrington, A. Forbes and J. F. Fulton among the neurophysiologists. I had great help in conversations with S. R. Cajal and R. Bárány and recently an intimate contact with the neurophysiological school of Washington University, chiefly with H. S. Gasser, A. S. Gilson and G. H. Bishop gave me valuable suggestions. These authors may find ideas in this paper they think their own. Perhaps it is so, but perhaps we arrived at them from different premises.

SUMMARY.

1. The structure of the primary acoustic nuclei has been studied in preparations stained with selective methods.

2. Each cochlear fibre gives branches to no less than thirteen regions of specific structure, where more than fifty different types of cells have been found. Each cochlear fibre establishes connections with hundreds of cells. Endogenous association fibres connect reciprocally the different parts of the primary nuclei.

3. The structure of each one of the thirteen regions is summarily described.

4. An attempt is made to determine the physiological significance of the anatomical structures.

5. The main conclusion is that the primary nuclei cannot be considered as "dead-beat" synapses, but rather as "selective" synapses, which transmit impulses according to: *1.* the afferent impulses; *2.* the impulses set up in the nuclei themselves by the cells with short axis-cylinder; *3.* the impulses arriving from the upper nuclei via the centrifugal fibres.

6. The necessity of carrying out a complete anatomical analysis of the central nuclei, in order to have a sound foundation for physiological research is stressed. Today no reflex arc and no part of the nervous system is sufficiently known.

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